



MODIFIED STEROIDS

RESUME

· THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

TO

THE ALIGARH MUSLIM UNIVERSITY, ALIGARH

SYED MASARRAT ALI

T-3444

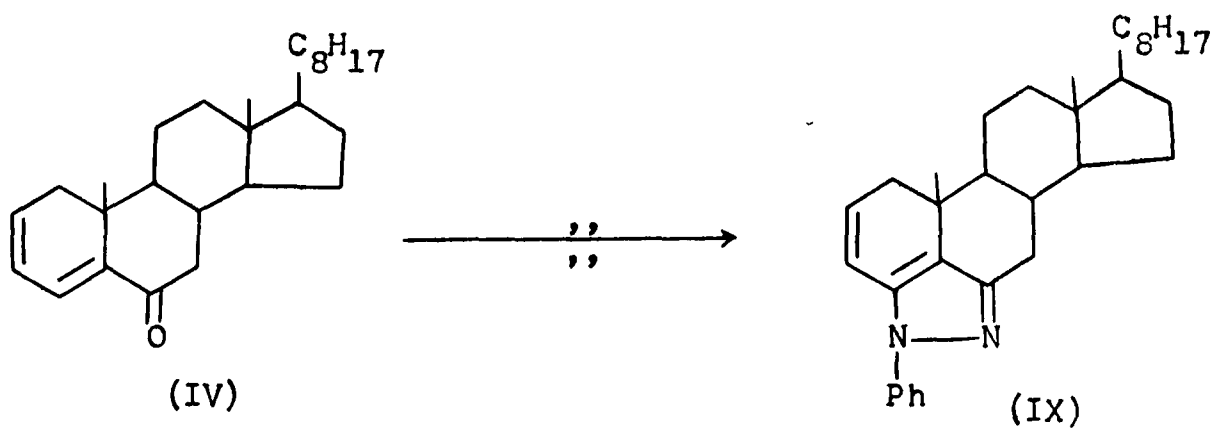
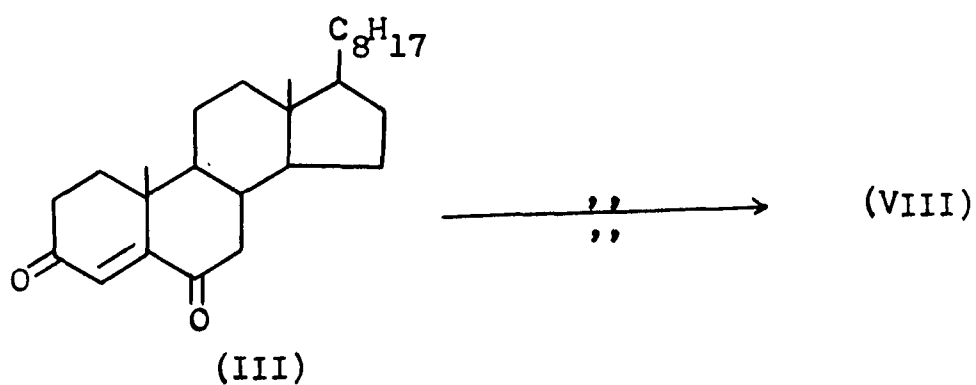
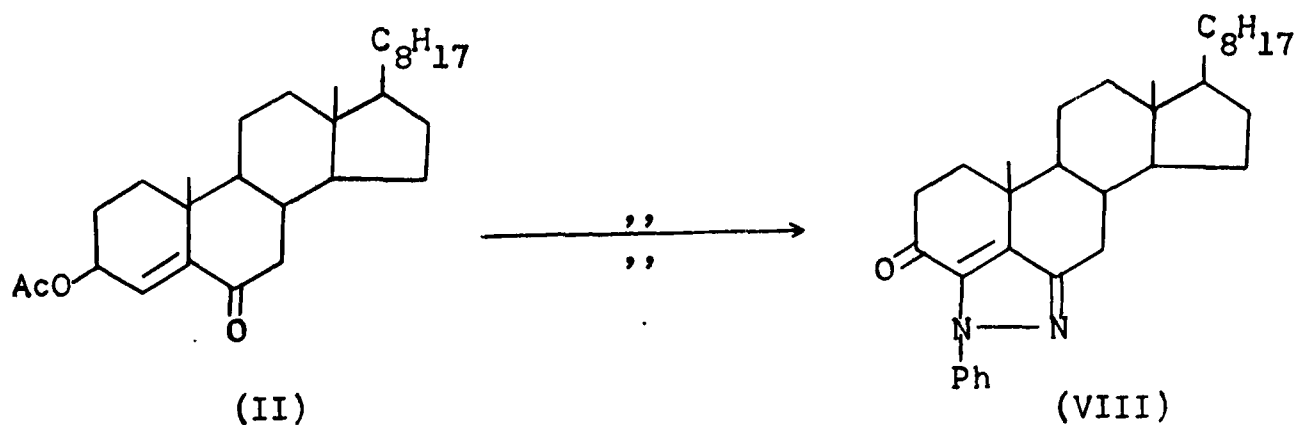
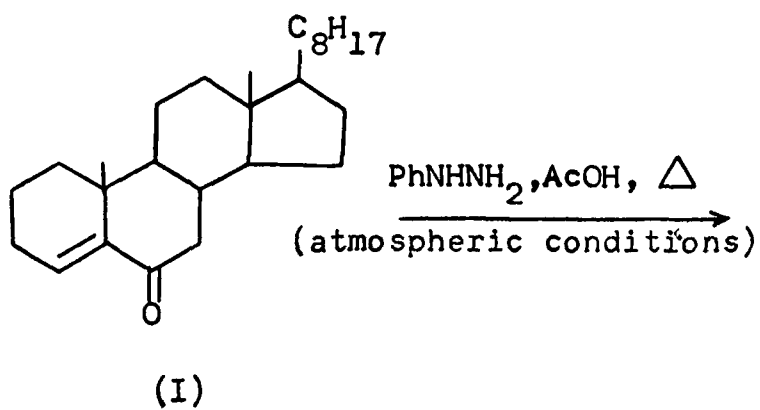
DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)

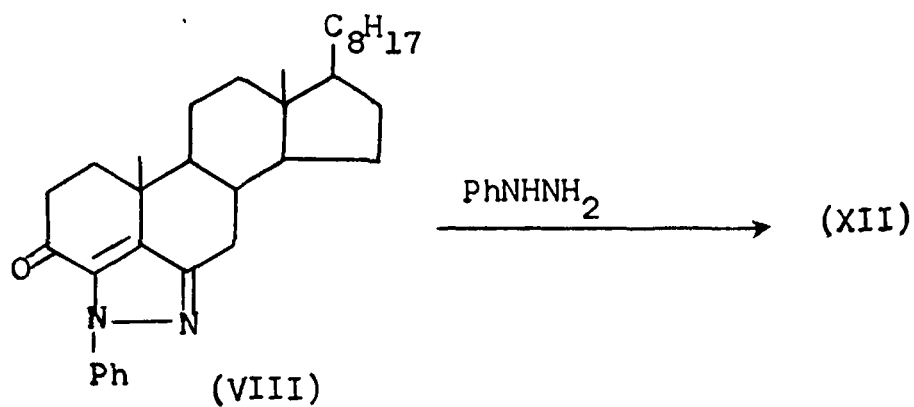
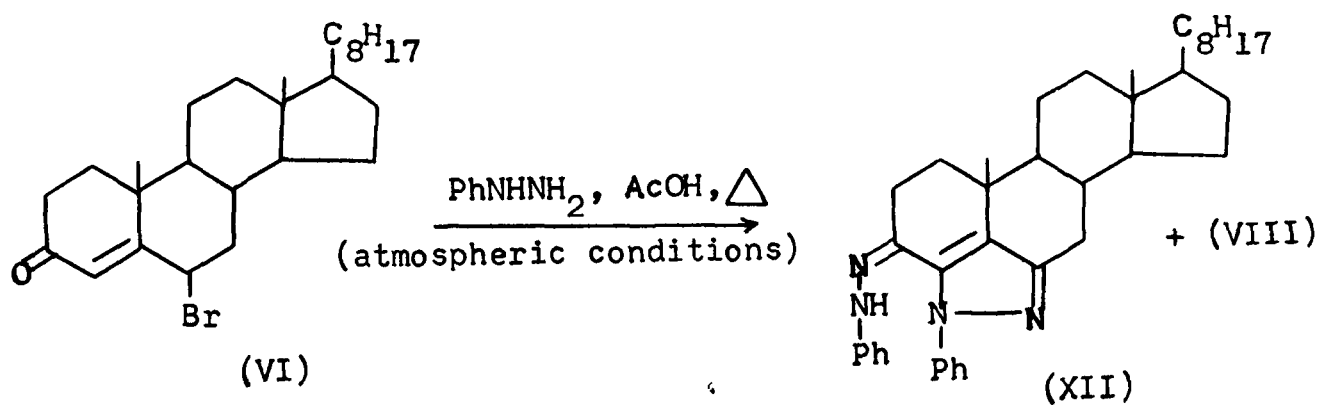
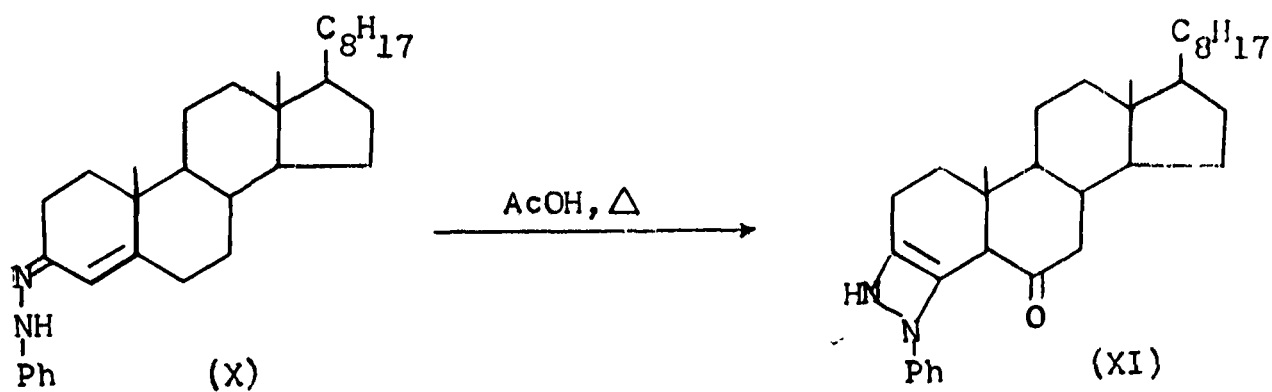
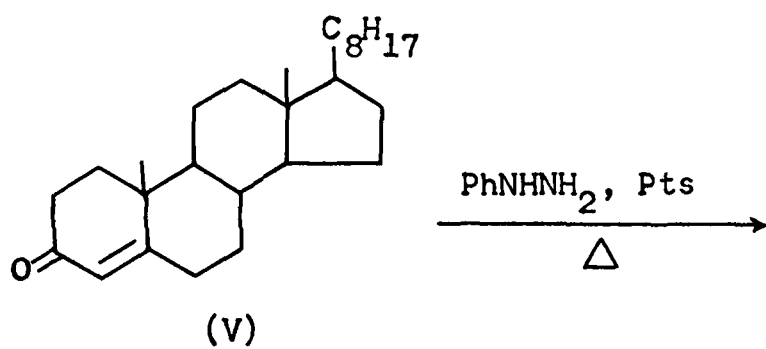
1986

STEROIDAL PYRAZOLES AND PYRAZOLINES

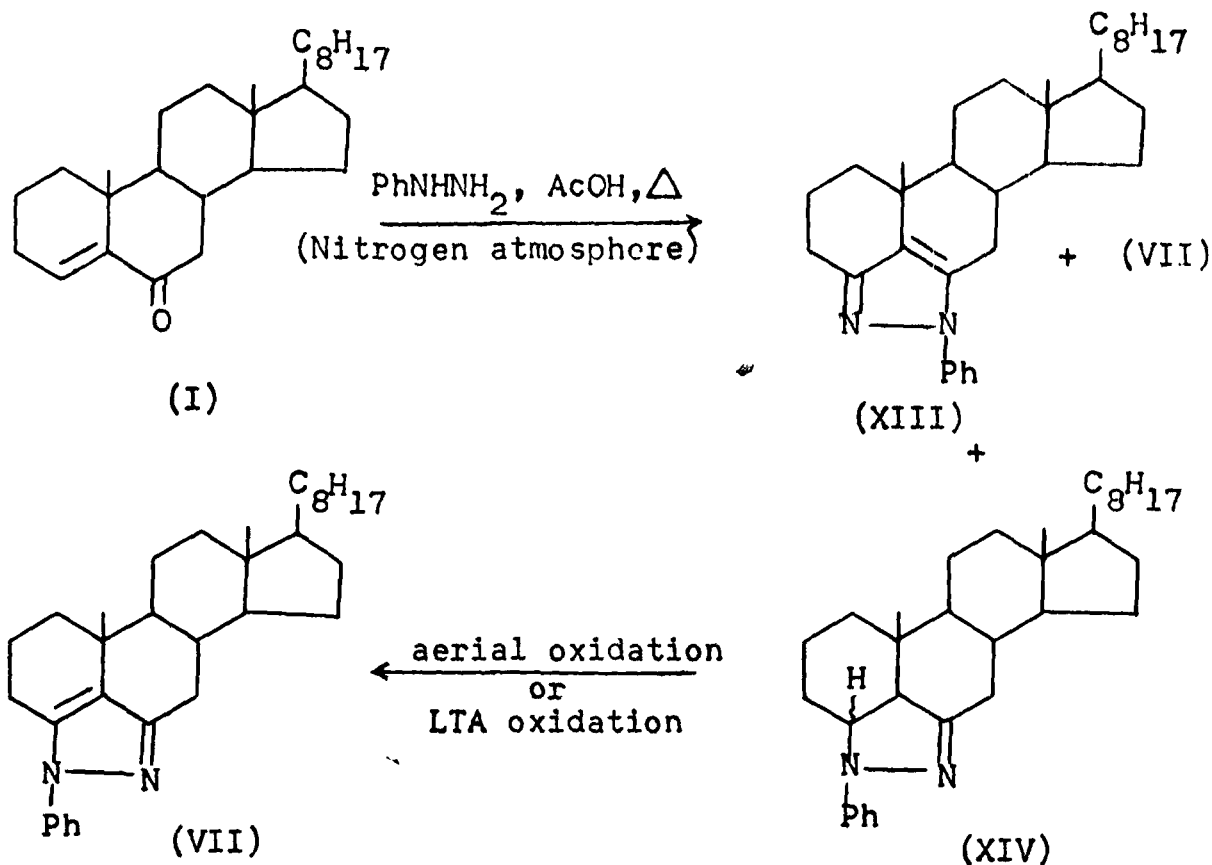
Most of the compounds containing pyrazole nucleus show remarkable and unusual, anabolic and physiological activities. This prompted the chemists for their synthesis and investigate such derivatives for their biological activities. Steroidal pyrazoles with varied biological activities have also been reported in the recent past. The most commonly used method for the purpose is the reaction of hydrazine or substituted hydrazine with α,β -unsaturated ketones.

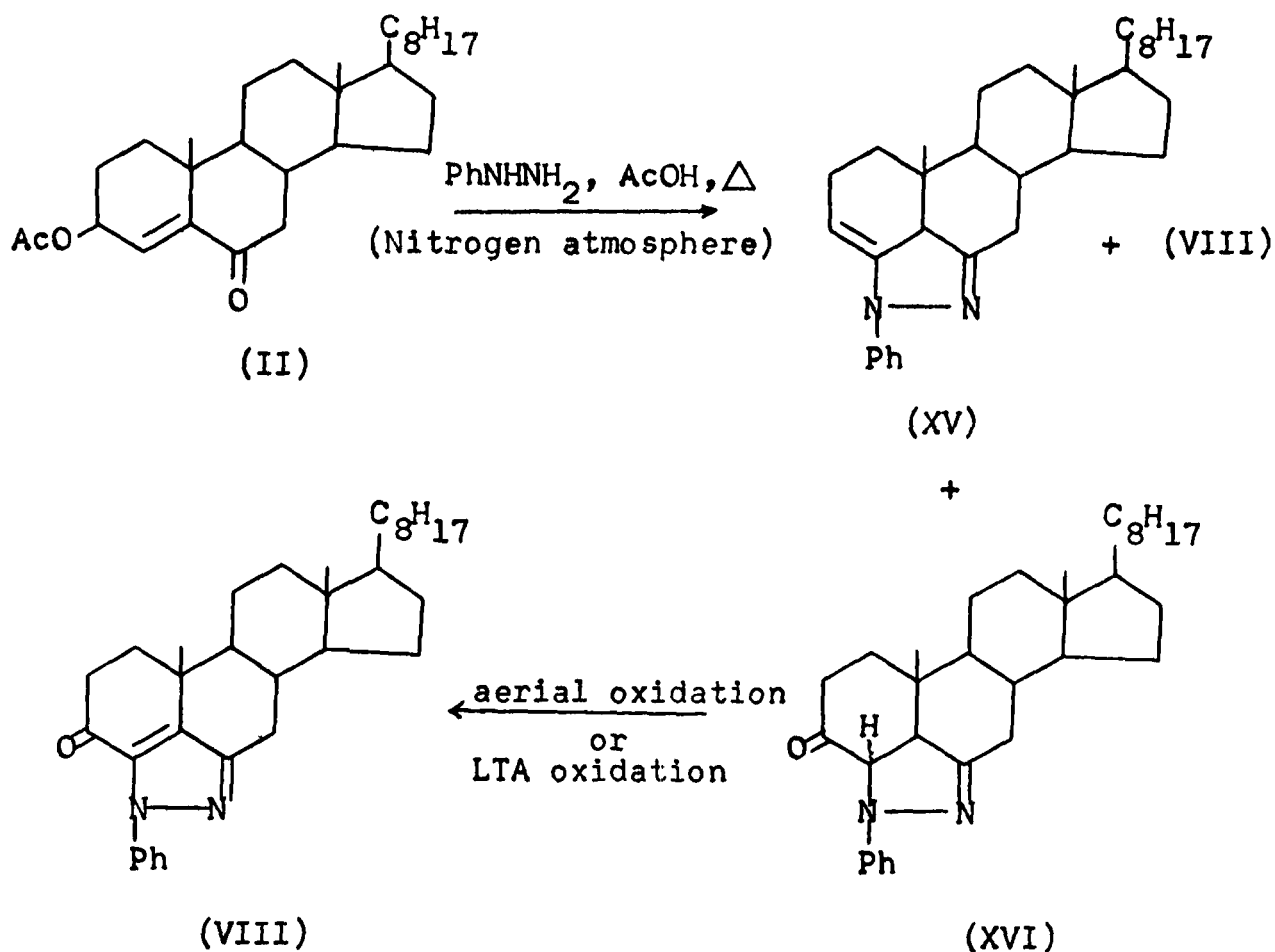
It is worth mentioning here that little attention has been paid towards the synthesis of steroidal pyrazoles in the cholestane and stigmastane series. Prompted by the results obtained earlier, we made attempts to synthesize steroidal pyrazoles from α,β -unsaturated ketones in the cholestane and stigmastane series. For the present study we treated some of the easily accessible α,β -unsaturated ketones such as 4-cholesten-6-one (I), 6-oxo-4-cholesten-3 β -yl acetate (II), 4-cholestene-3,6-dione (III), 2,4-cholestadien-6-one (IV), 4-cholesten-3-one (V), and 6 β -bromo-4-cholesten-3-one (VI) with phenylhydrazine under atmospheric conditions. These results are summarized below.



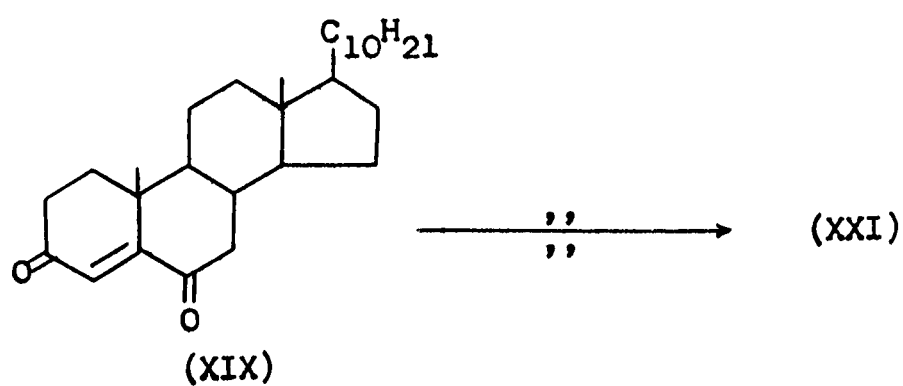
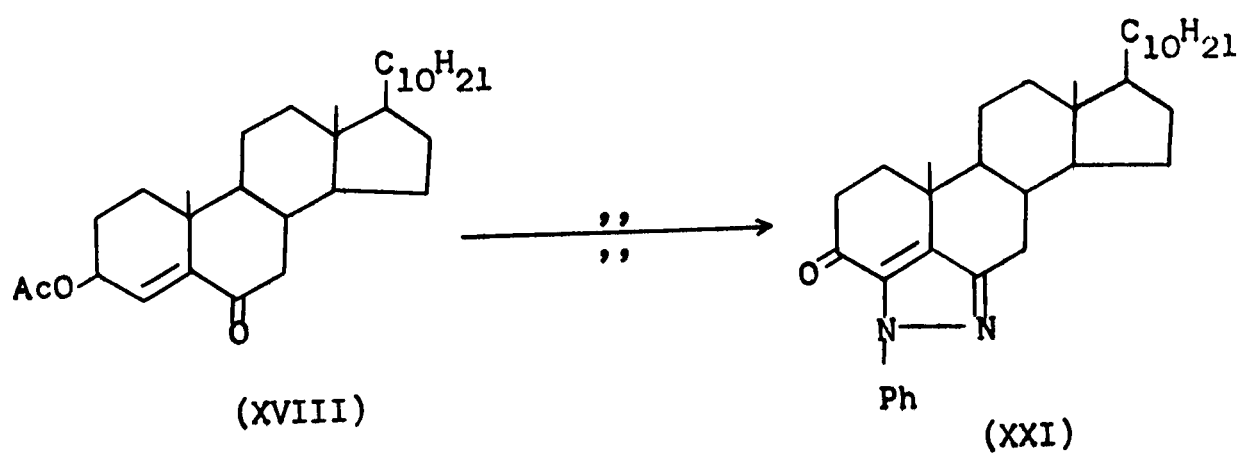
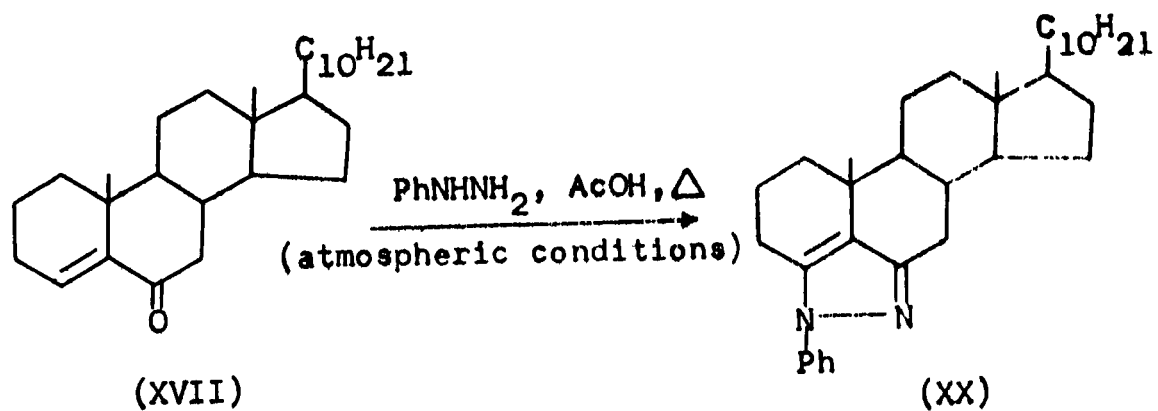


The reaction of the ketones (I) and (II) with phenylhydrazine was also carried out under nitrogen atmosphere. The observation that expected pyrazolines (XIV) and (XVI) respectively are obtained as the products supported the involvement of atmospheric oxygen for the oxidation of pyrazoline to give pyrazoles. This has further been substantiated by the conversion of pyrazolines (XIV) and (XVI) to pyrazoles by aerial oxidation or by treatment with lead tetraacetate.



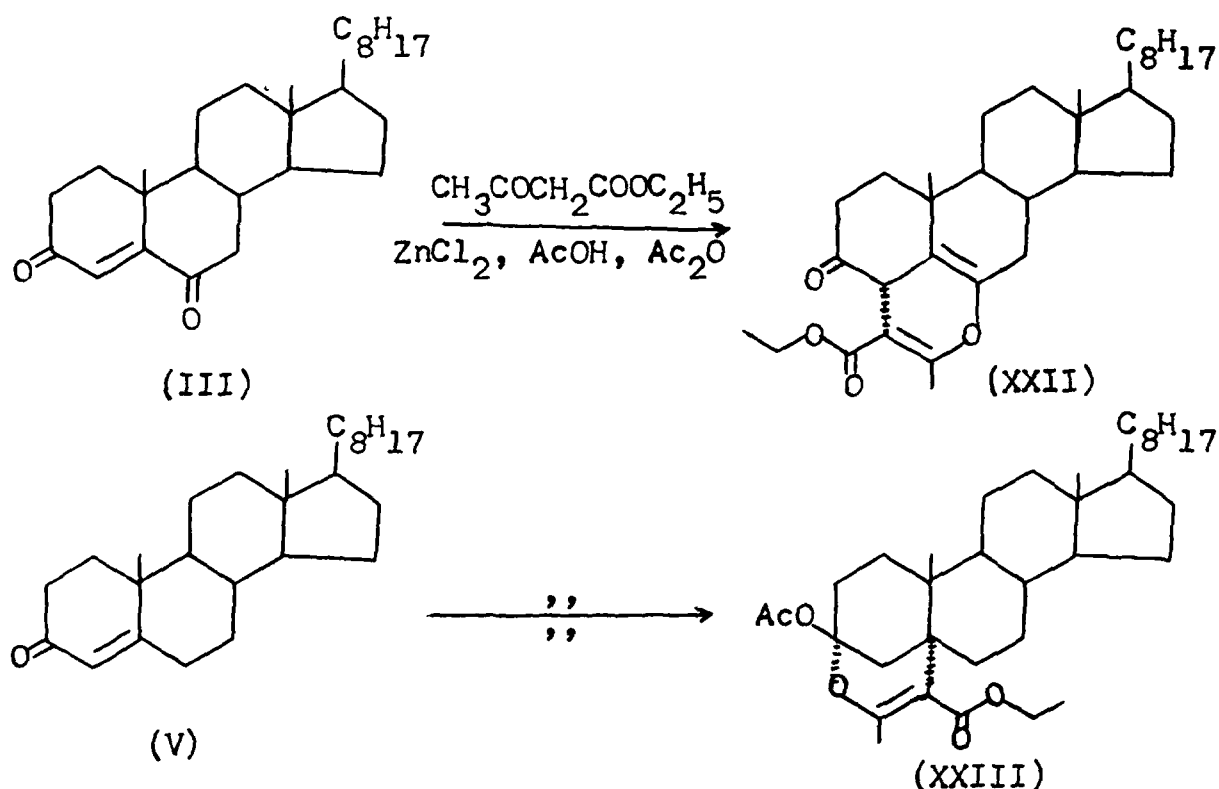


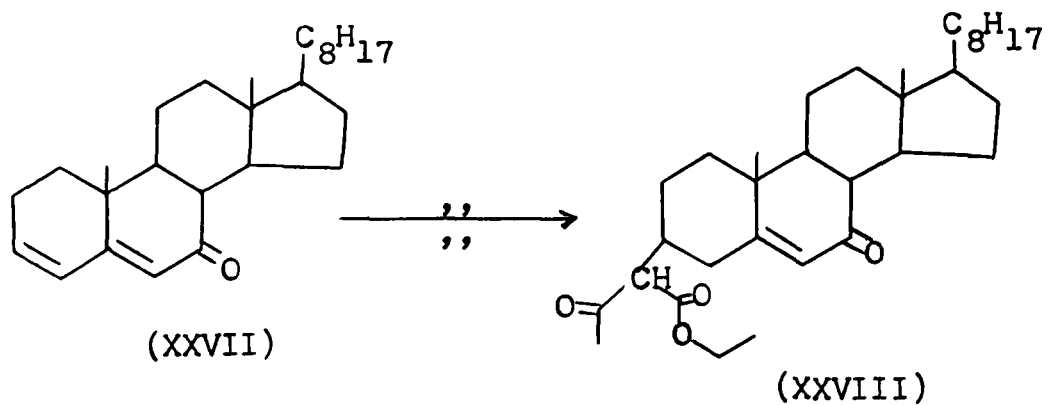
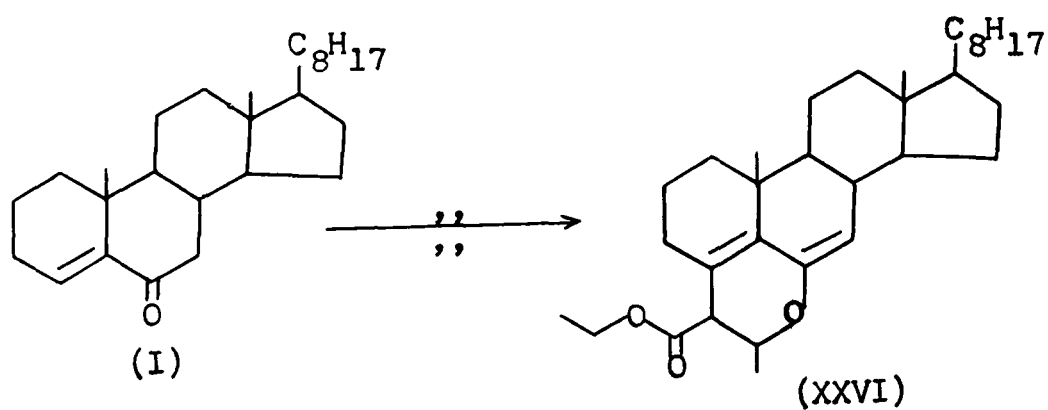
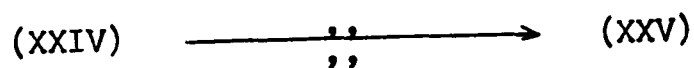
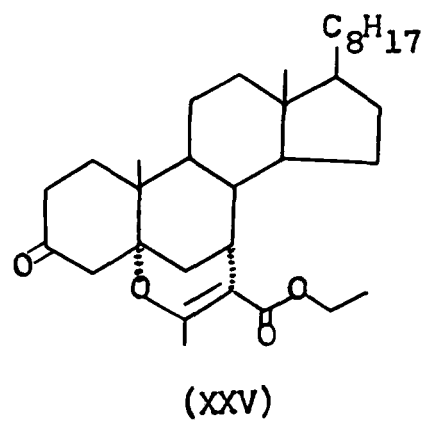
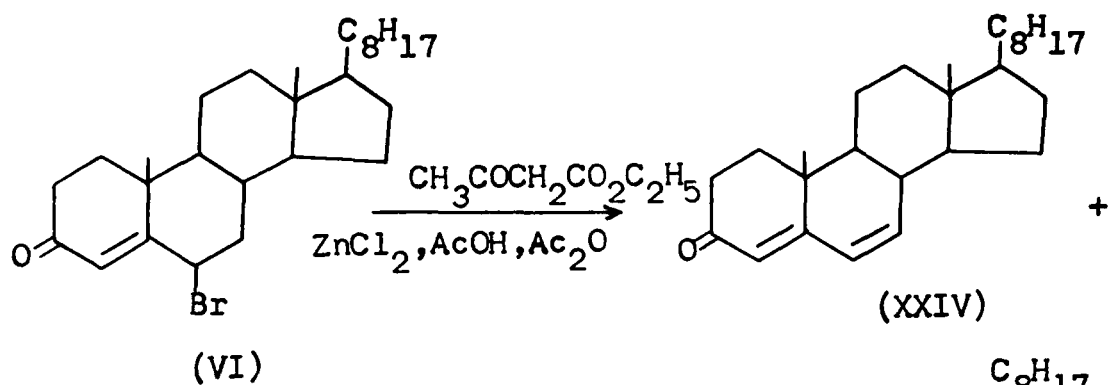
In order to assess the consistency of the reaction between steroidal α,β -unsaturated ketones and phenylhydrazine leading to pyrazoles, it was considered desirable to extend this study on to the stigmastane series. For this purpose 4-stigmasten-6-one (XVII), 6-oxo-4-stigmasten-3 β -yl acetate (XVIII) and 4-stigmastene-3,6-dione (XIX) were treated with phenylhydrazine. The results summarized below are consistent with the earlier observations made in the cholestane series.



STEROIDAL PYRANS

Compounds containing pyran, dihydropyran or pyrone moiety show high antiallergic, cytotoxicity and/or antitumor activity. Many workers reported the synthesis of pyrans by the reaction of α,β -unsaturated ketones and ethylacetoacetate. Survey of the literature revealed that applicability of these reactions to the steroidal substrates seems to be overlooked. Hence with a view of synthesizing pyrans in the steroidal systems we carried out the reactions of some of the easily accessible α,β -unsaturated ketones in the cholestane series with ethylacetoacetate in the presence of zinc chloride acetic acid and acetic anhydride. The following chart shows the reactions of the various α,β -unsaturated ketones (I, III, V, VI, XXIV and XXVII) with ethylacetoacetate.

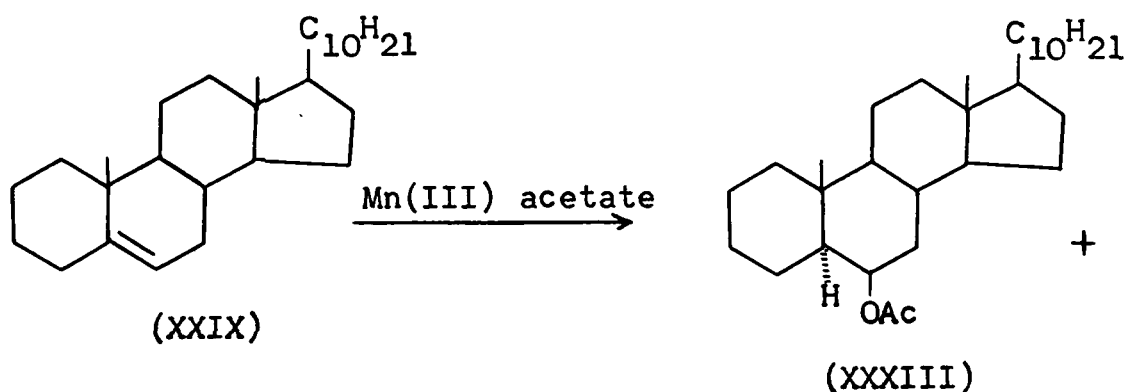


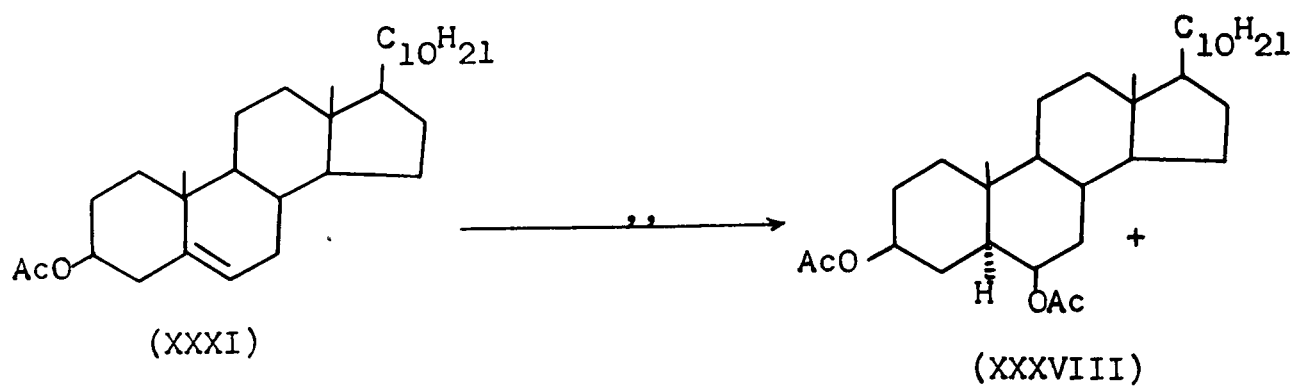
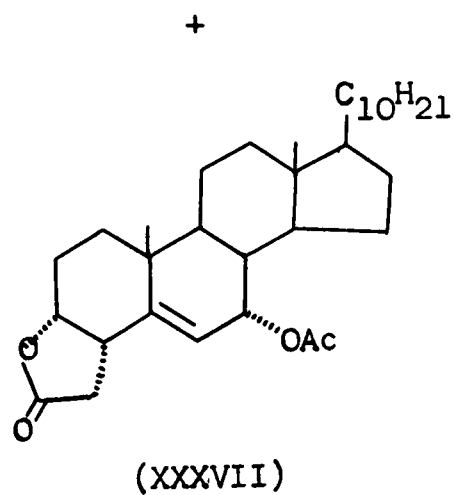
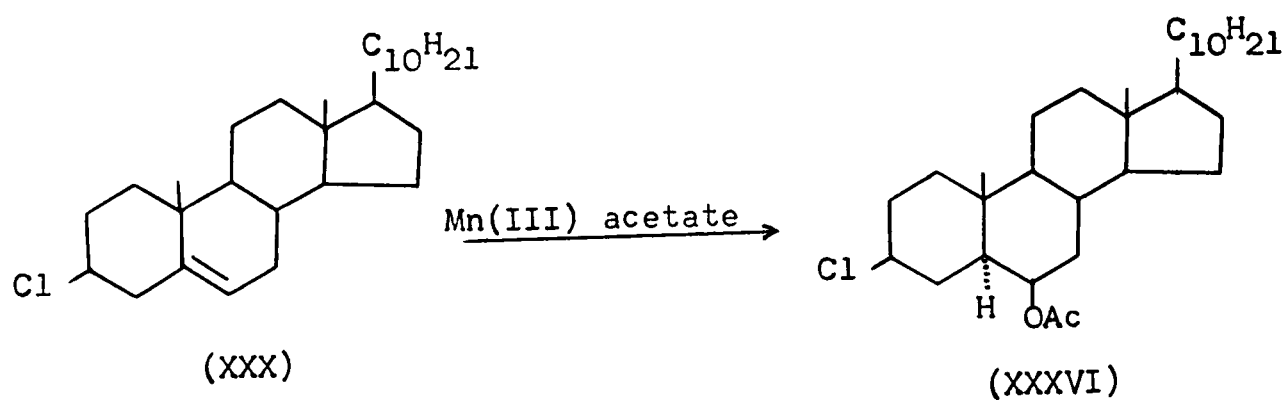
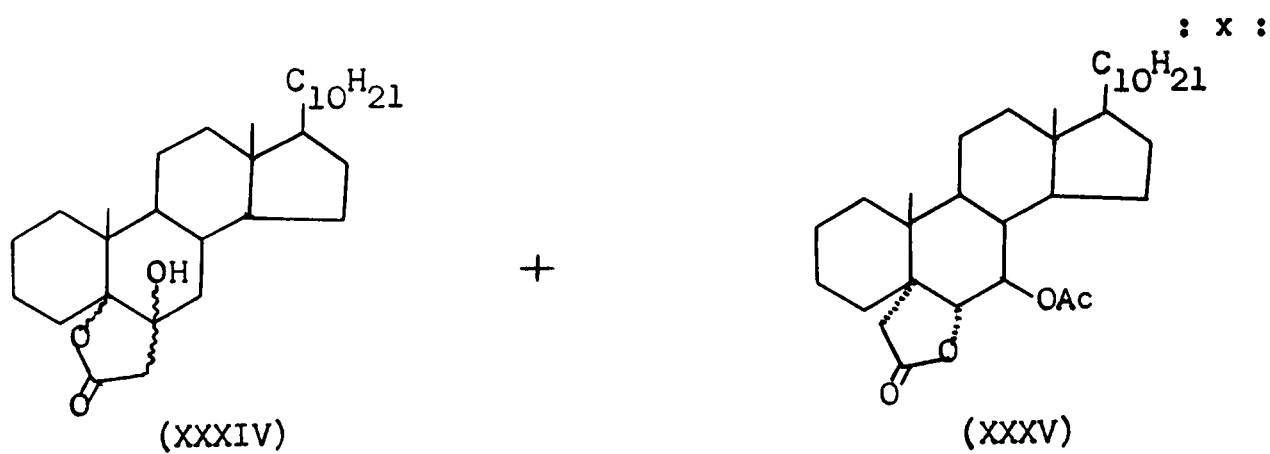


OXIDATION OF STEROIDAL OLEFINS WITH Mn(III) ACETATE

The oxidation of olefins with Mn(III) acetate has been studied extensively, which leads to the formation of γ -lactones alongwith other side products. Recently the synthesis of γ -lactones has attracted the attention of organic chemists for their potentialities as allergenic, growth inhibitor, antibacterial and antitumor activity. (Reaction of Mn(III) acetate with steroidal olefins has remained by large unexplored.

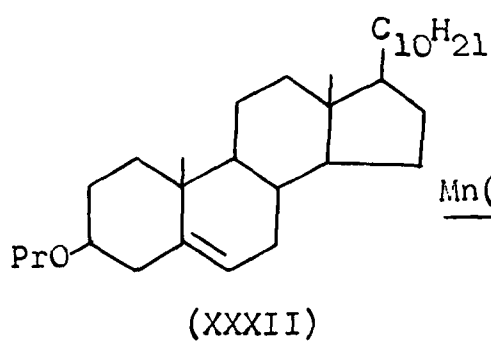
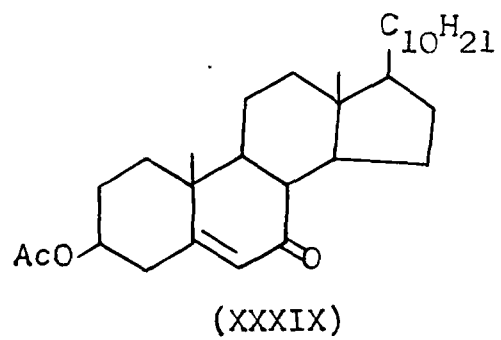
Recently the formation of γ -lactones in the cholestane series has been reported from our laboratory by the oxidation with Mn(III) acetate in the presence of acetic acid and propionic acid. As an extension 5-stigmastene (XXIX), 5-stigmasten-3 β -yl chloride (XXX), 5-stigmasten-3 β -yl acetate (XXXI) and 5-stigmasten-3 β -yl propionate (XXXII) were subjected to the similar reaction conditions. The products obtained have been summarized in the following table.



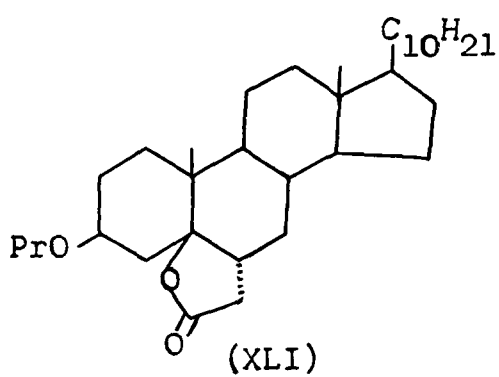
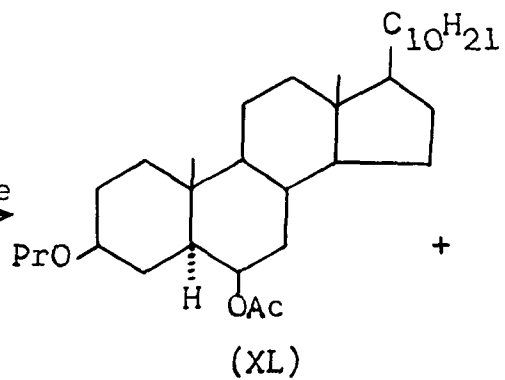


(XXXVII)

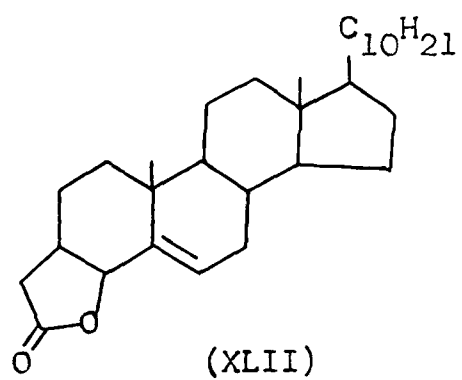
+



Mn(III) acetate

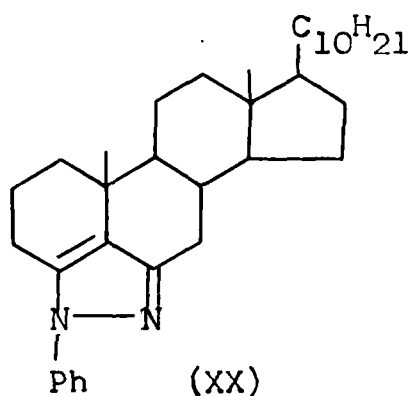
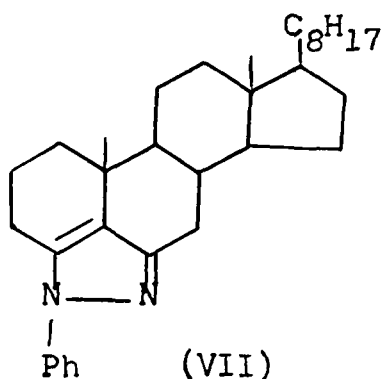


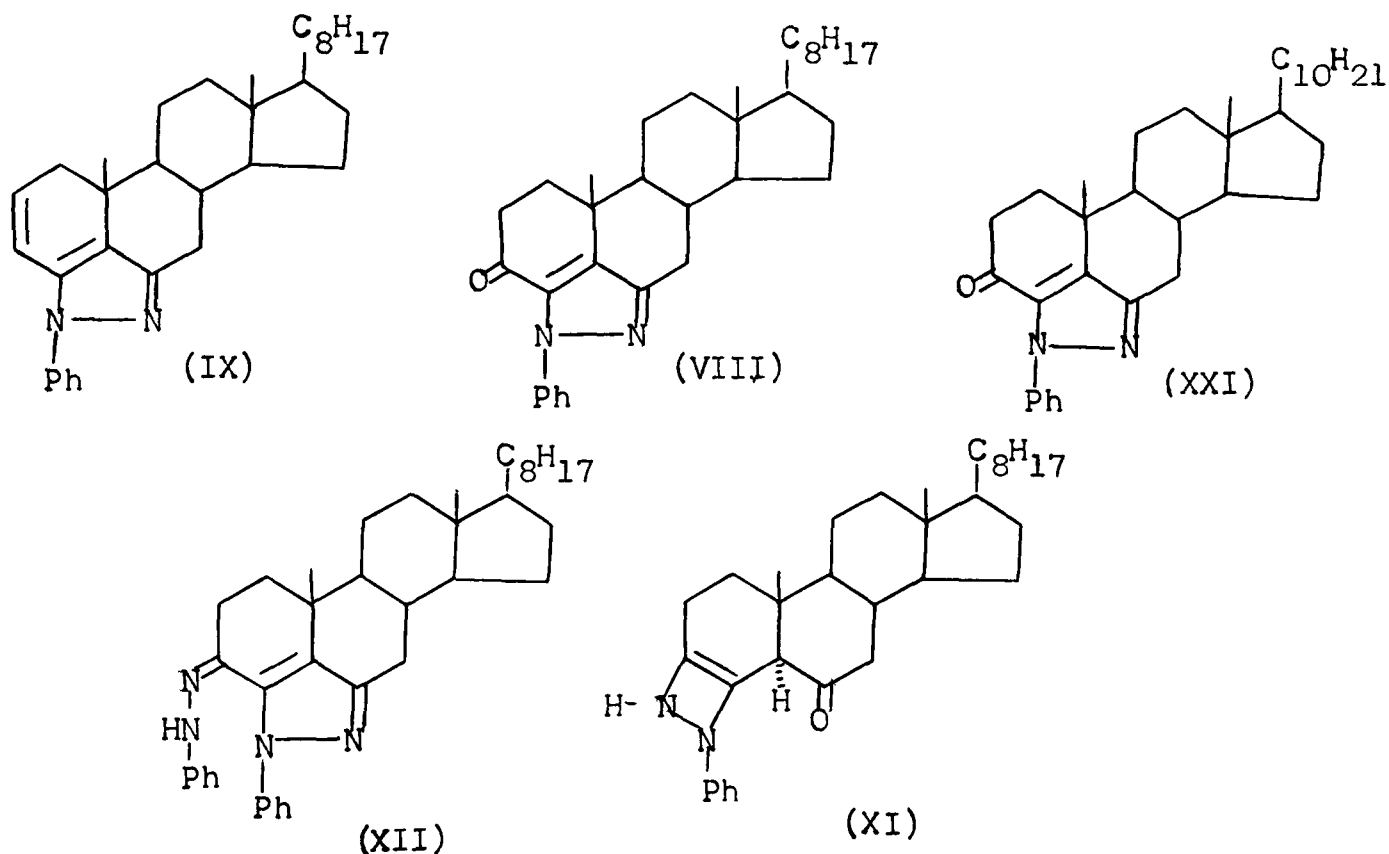
+



MASS SPECTRAL STUDIES ON STEROIDAL COMPOUNDS(a) Steroidal pyrazoles

A survey of the literature revealed that no systematic mass spectral study of steroidal pyrazoles has been reported. In the previous part we have described the preparation of a number of steroidal pyrazoles. These two events prompted us to examine the mass spectra of several structurally related steroidal pyrazoles. These include 2'-phenyl-4-cholesteno[4,6-cd]pyrazole (VII), 2'-phenyl-4-stigmasteno[4,6-cd]pyrazole (XX), 2'-phenyl-2,4-cholestadieno[4,6-cd]pyrazole (IX), 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]pyrazole (VIII), 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]pyrazole (XXI), 2'-phenyl-4-cholesteno[4,6-cd]pyrazole-3-one phenylhydrazone (XII) and 6-oxo-5 α -3-cholesteno[3,4]N,N-phenylhydrazine (XI). These compounds are structurally very close to each other. It was anticipated that they will follow similar fragmentation pattern thus offering a simple and effective method for their characterization by mass spectrometry.

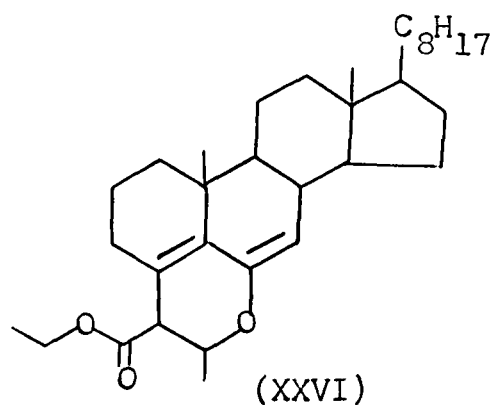
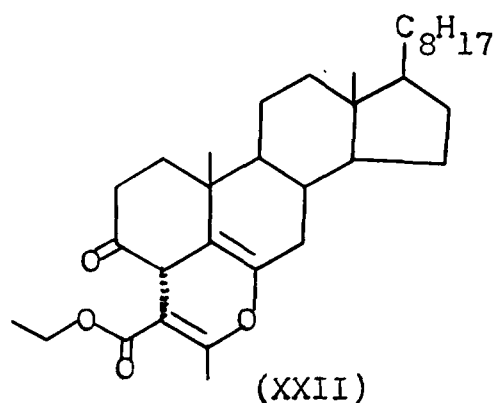




A comparison of mass spectra of pyrazoles (VII, XX, IX, VIII, XXI and XII) clearly showed remarkable similarity between them. These six pyrazoles represent changes in the different parts of the molecule which can be made use of in the interpretation of the spectra. Screening of these spectra revealed that these steroidal pyrazoles undergo characteristic fragmentation which can be exploited for identification purposes.

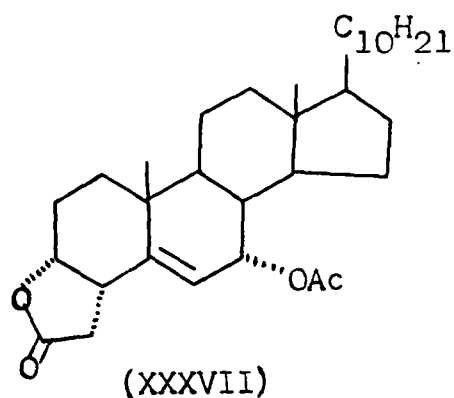
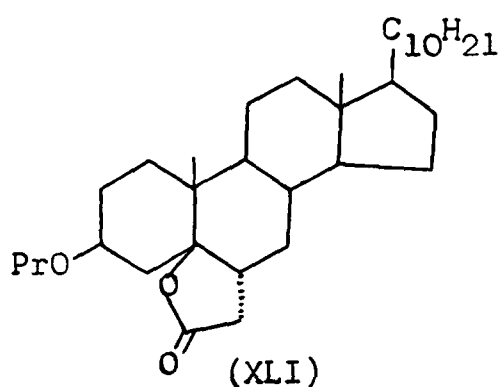
(b) Steroidal pyrans

A survey of the literature revealed that no mass spectral study of steroid al pyrans has been reported though mass spectra of several pyrans have been examined. The present chapter, as an initial chapter is concerned with a very limited number of steroid al pyrans such as 2'-methyl-3'-carboethoxy-3-oxo-5-cholesteno[4,6-de]- γ -pyran (XXII) and 2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydropyran (XXVI). Furthermore, these pyrans are not structurally very closely related to each other and therefore, their mass spectral study has very limited scope under the circumstances. Nevertheless we considered it necessary and interesting to look into the mass spectra of these compounds.



(c) Steroidal γ -lactones

The concluding part of the chapter deals with the mass spectral study of two γ -lactones, belonging to the stigmastane series. They are 3β -propionoxy- 5β -hydroxystigmast- 6α -yl acetic acid γ -lactone (XLI) and 7α -acetoxy- 3α -hydroxystigmast- 5 -en- 4α -yl acetic acid γ -lactone (XXXVII). In an earlier work from our laboratory mass spectra of several γ -lactones belonging to the cholestane series have been examined. It may be pointed out that the main idea at present is to compare the spectra of the γ -lactones in the two series, namely the cholestane and the stigmastane series.





MODIFIED STEROIDS

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

TO

THE ALIGARH MUSLIM UNIVERSITY, ALIGARH

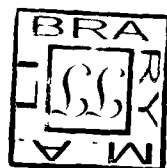
SYED MASARRAT ALI

DEPARTMENT OF CHEMISTRY

ALIGARH MUSLIM UNIVERSITY

ALIGARH (INDIA)

1986



T3444

Dr. M. S. Ahmad


M. Sc., Ph. D. (Manchester)
Professor of Chemistry



Aligarh Muslim University
Department of Chemistry
ALIGARH-202001 INDIA

Dated

This is to certify that the work embodied in this thesis entitled, 'Modified Steroids' is the original work of Mr. Syed Masarrat Ali accomplished under my supervision. The thesis is suitable for the submission for the award of the degree of Doctor of Philosophy in Chemistry.


(M.S. Ahmad)
Professor and Chairman
Department of Chemistry
A.M.U. ALIGARH

ACKNOWLEDGEMENTS

It is difficult for me to find proper expression of my heartfelt sense of gratitude to Professor M. Shahabuddin Ahmad, Dean Faculty of Science, Chairman Department of Chemistry for his constant help, unabated interest and all possible facilities. It is only due to his everlasting encouragement, constructive criticism and zealous efforts that the present work has taken the final shape. Thanks are also due to Professor Wasiur Rehman, Pro-Vice Chancellor, Aligarh Muslim University, ex-Chairman Department of Chemistry for providing facilities.

I would like to make a thankful note of Dr. M. Mushfiq, who has always been of great help and source of inspiration especially at the difficult times during the project. I also thankfully recognize the efforts of Mr. Tanveer Shaukat Siddiqui who strained himself in drawing the mass spectra. My colleagues deserve a great many thanks for they stood by me throughout. The execution of uphill task of typing by Mr. Sabir Husain Siddiqui is gratefully acknowledged.

Finally, I am grateful to Council of Scientific and Industrial Research for providing financial assistance.


(Syed Masarrat Ali)

| CONTENTS

Contents

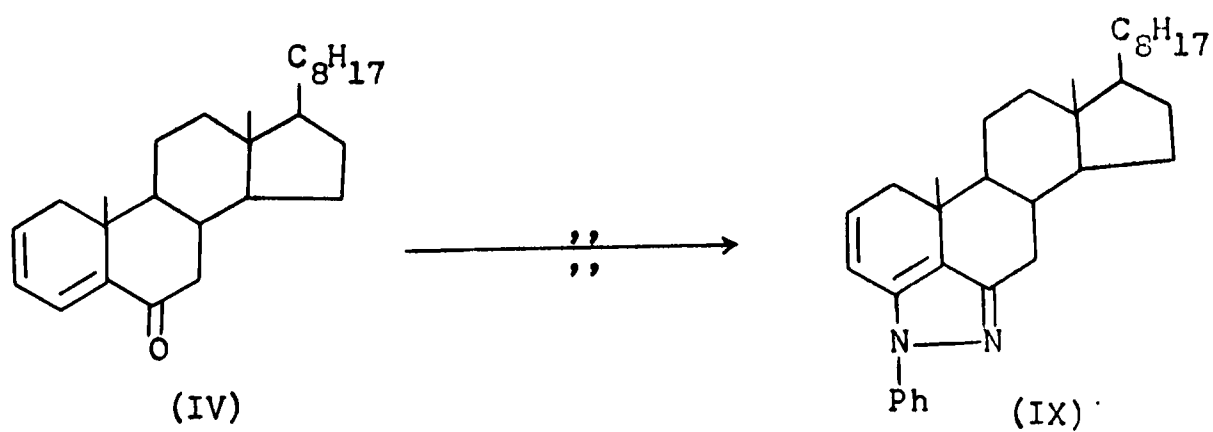
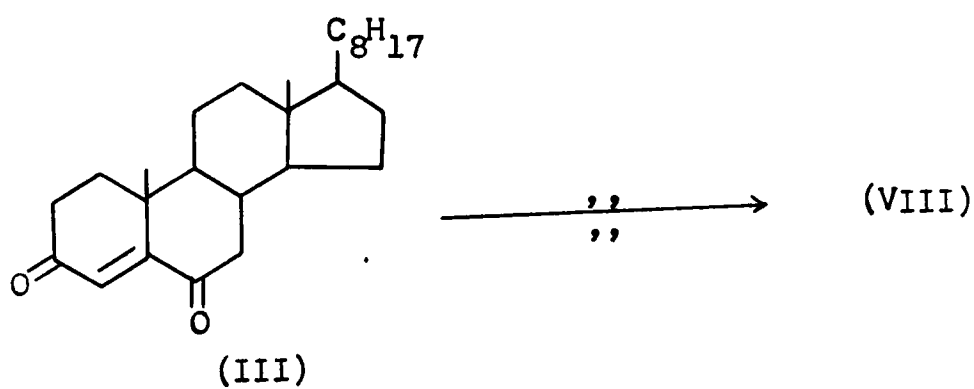
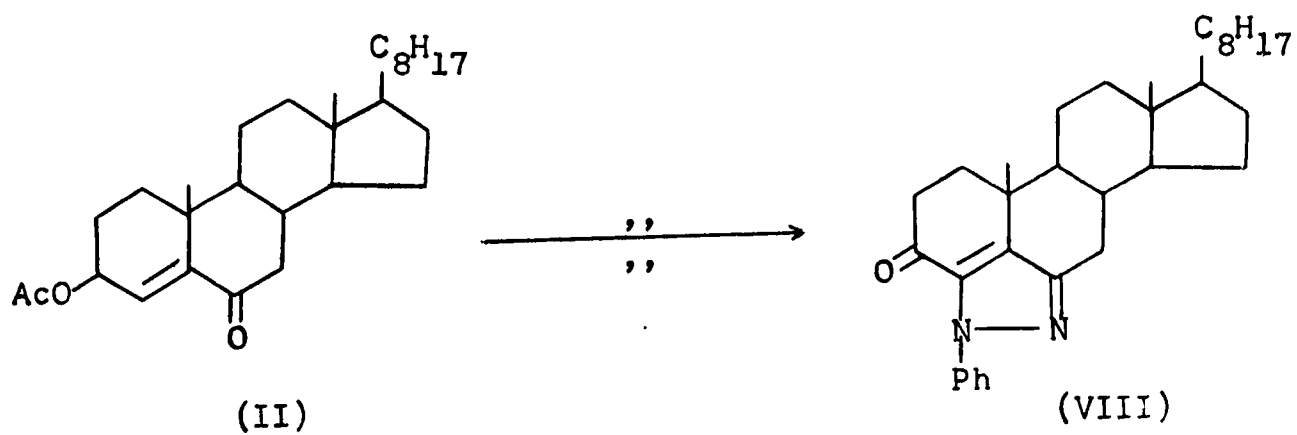
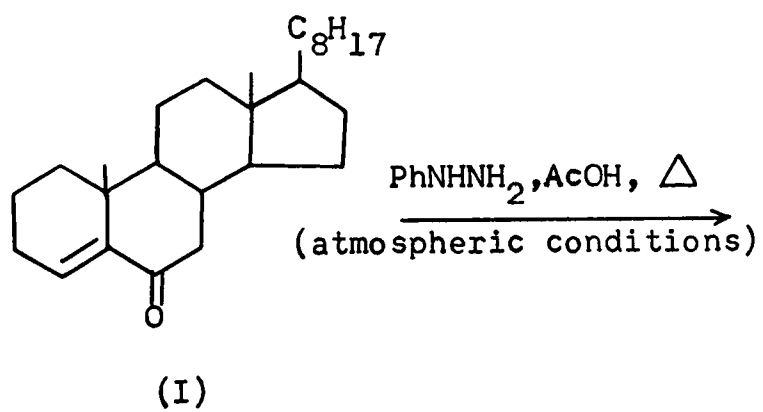
	<u>Page No.</u>
Summary	i-xv
Theoretical	1- 62
Part I : Pyrazoles	1- 28
Part II : Pyrans	29- 50
Part III: Oxidation of olefins with Mn(III) acetate	51- 62
Discussion	63-188
Part I : Steroidal pyrazoles and pyrazolines	63-100
Part II: Steroidal pyrans	101-119
Part III: Oxidation of steroidal olefins with Mn(III) acetate	120-143
Part IV : Mass spectral studies on steroidal compounds	144-188
Experimental	189-236
Part I :	189-215
Part II :	216-222
Part III:	223-228
Part IV :	229-236
References	237-245

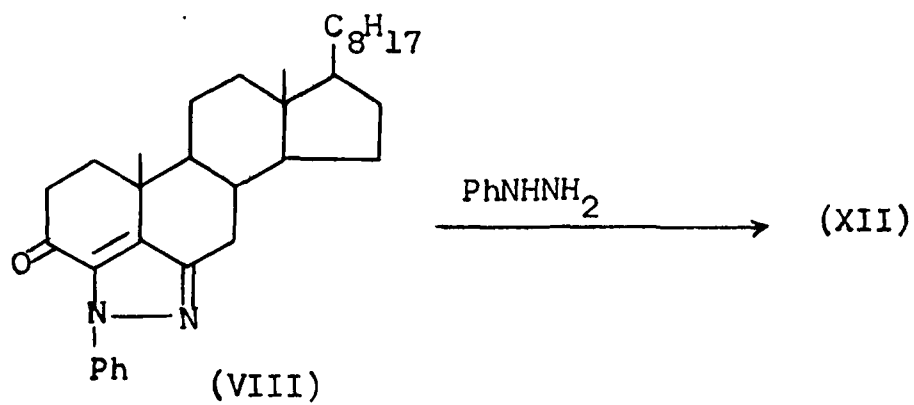
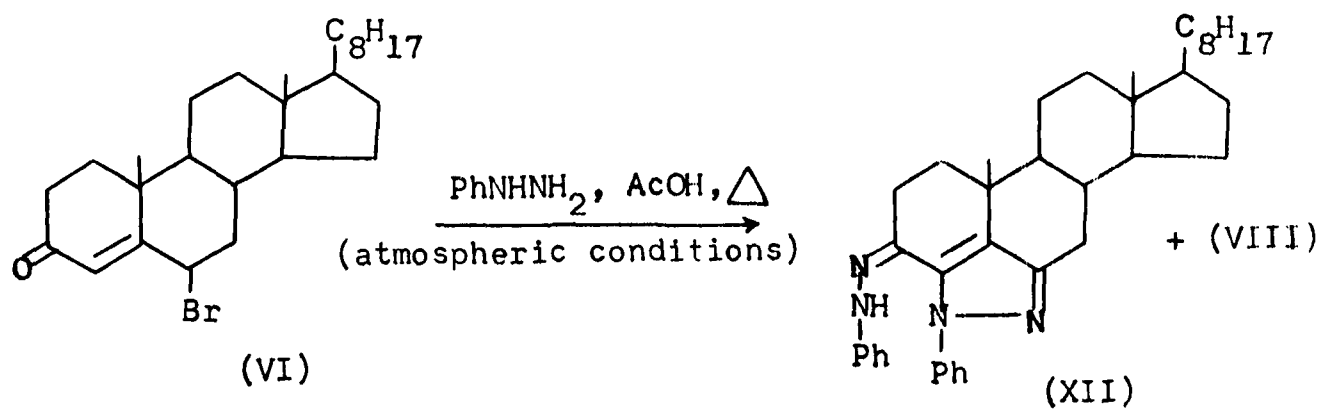
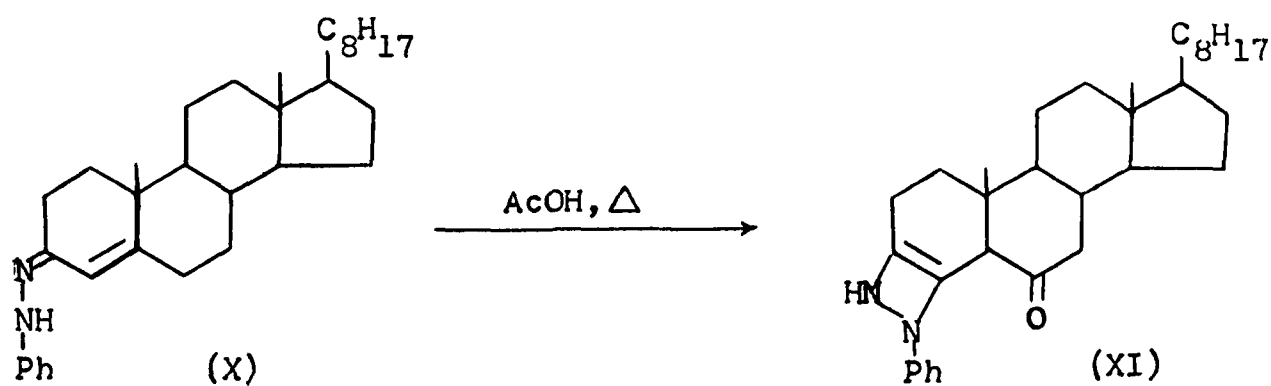
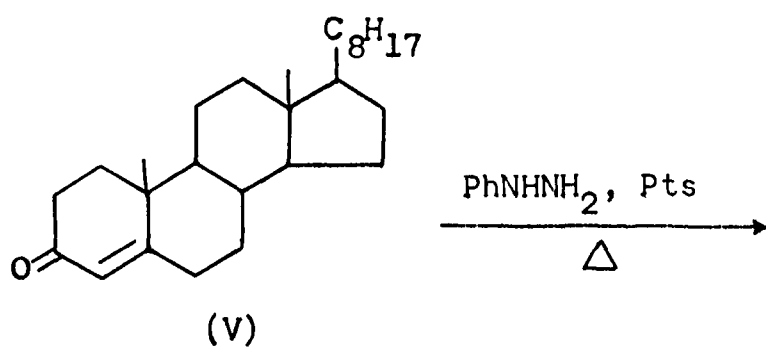
SUMMARY

STEROIDAL PYRAZOLES AND PYRAZOLINES

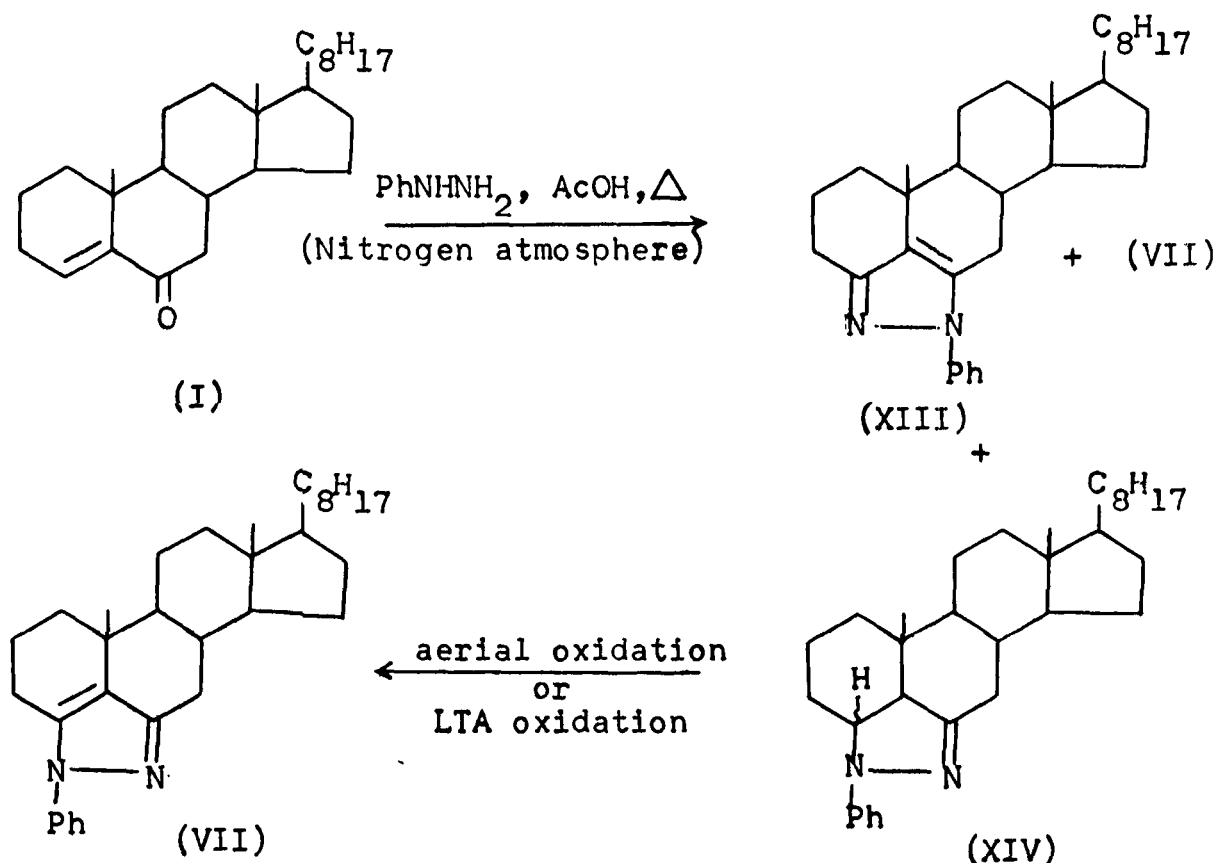
Most of the compounds containing pyrazole nucleus show remarkable and unusual, anabolic and physiological activities. This prompted the chemists for their synthesis and investigate such derivatives for their biological activities. Steroidal pyrazoles with varied biological activities have also been reported in the recent past. The most commonly used method for the purpose is the reaction of hydrazine or substituted hydrazine with α,β -unsaturated ketones.

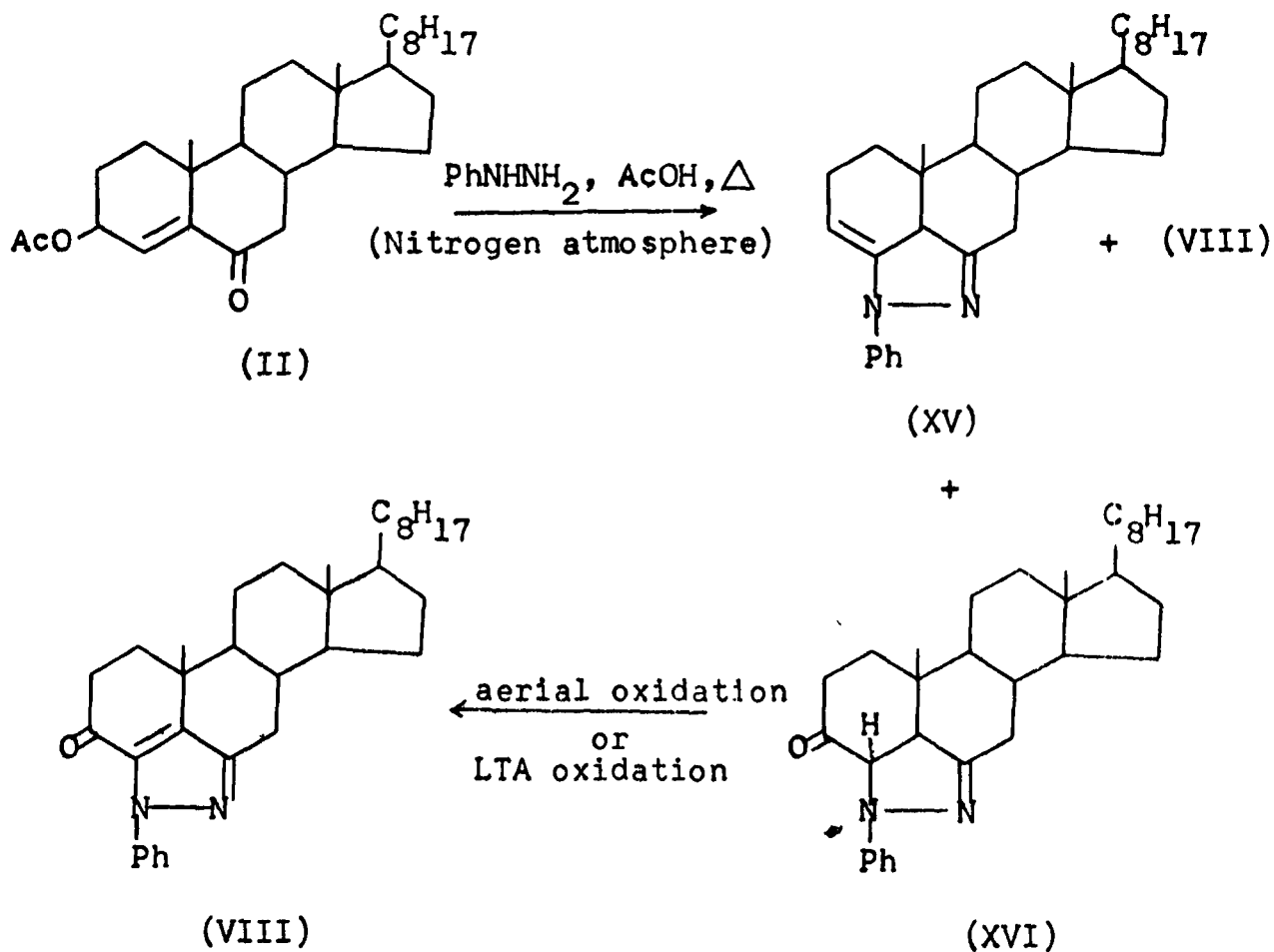
It is worth mentioning here that little attention has been paid towards the synthesis of steroidal pyrazoles in the cholestane and stigmastane series. Prompted by the results obtained earlier, we made attempts to synthesize steroidal pyrazoles from α,β -unsaturated ketones in the cholestane and stigmastane series. For the present study we treated some of the easily accessible α,β -unsaturated ketones such as 4-cholesten-6-one (I), 6-oxo-4-cholesten-3 β -yl acetate (II), 4-cholestene-3,6-dione (III), 2,4-cholestadien-6-one (IV), 4-cholesten-3-one (V), and 6 β -bromo-4-cholesten-3-one (VI) with phenylhydrazine under atmospheric conditions. These results are summarized below.



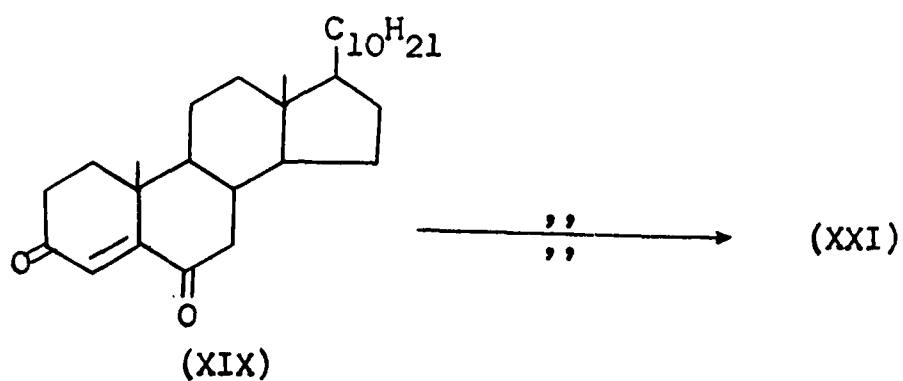
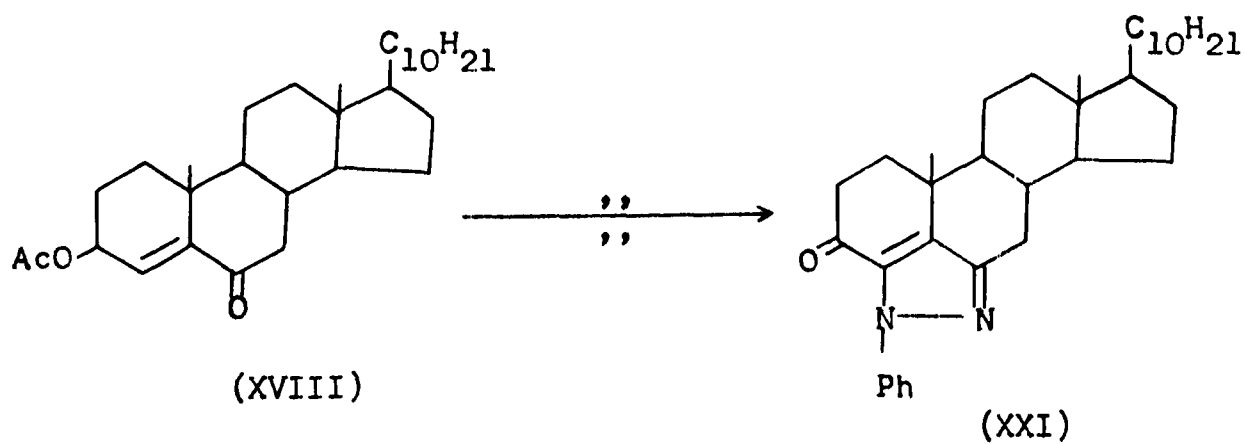
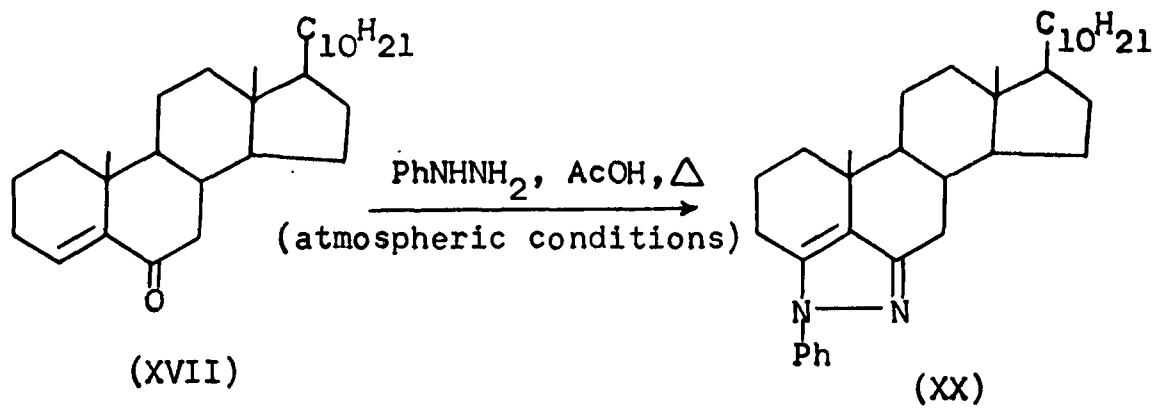


The reaction of the ketones (I) and (II) with phenylhydrazine was also carried out under nitrogen atmosphere. The observation that expected pyrazolines (XIV) and (XVI) respectively are obtained as the products supported the involvement of atmospheric oxygen for the oxidation of pyrazoline to give pyrazoles. This has further been substantiated by the conversion of pyrazolines (XIV) and (XVI) to pyrazoles by aerial oxidation or by treatment with lead tetraacetate.



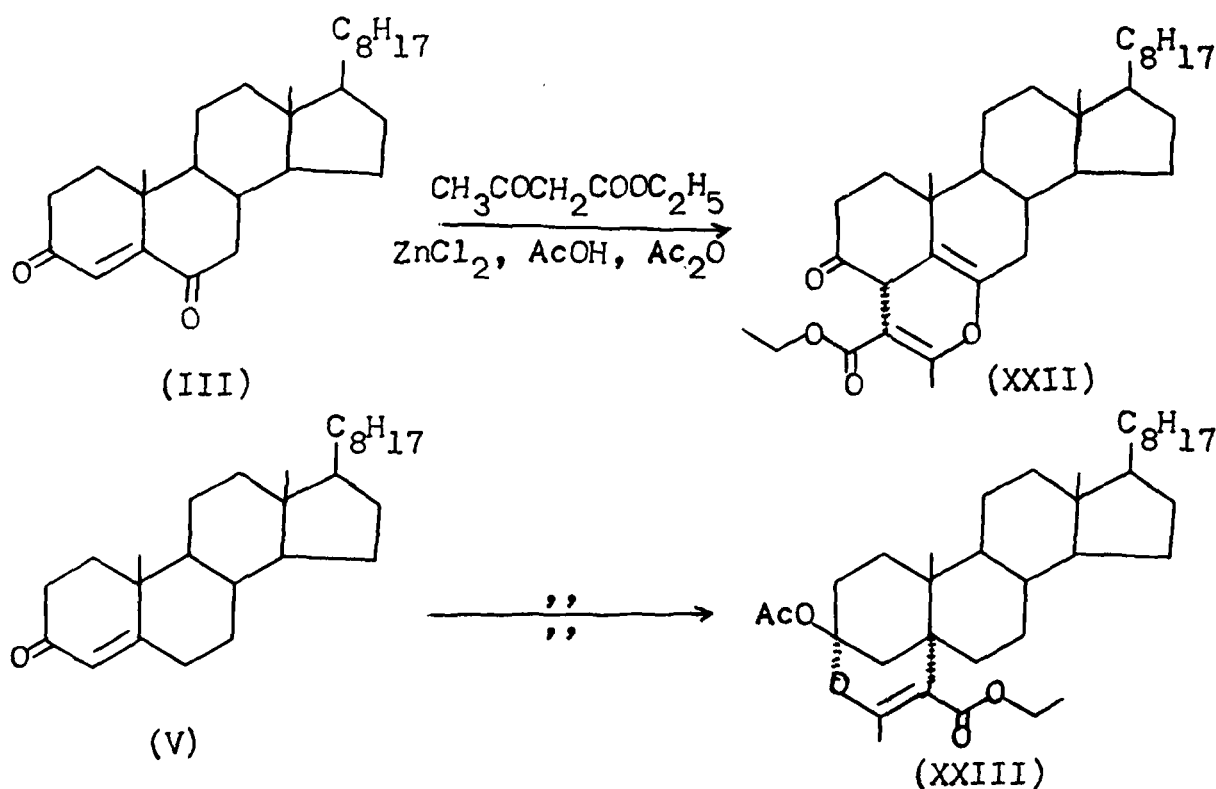


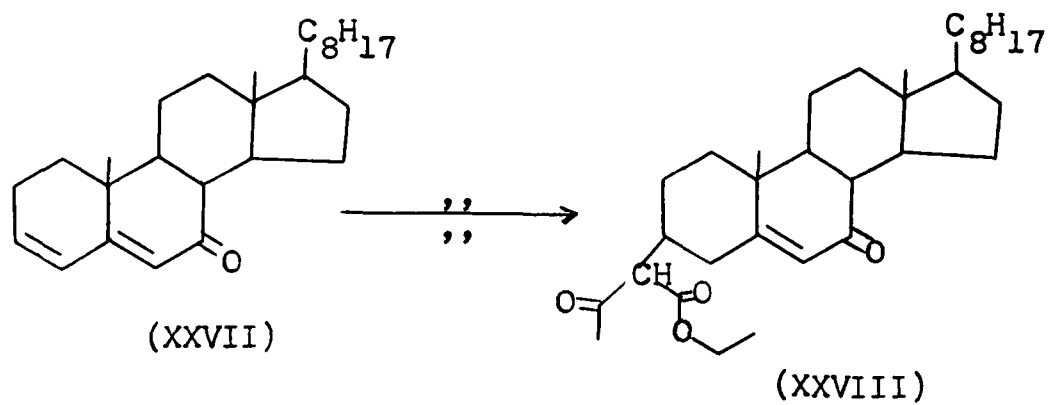
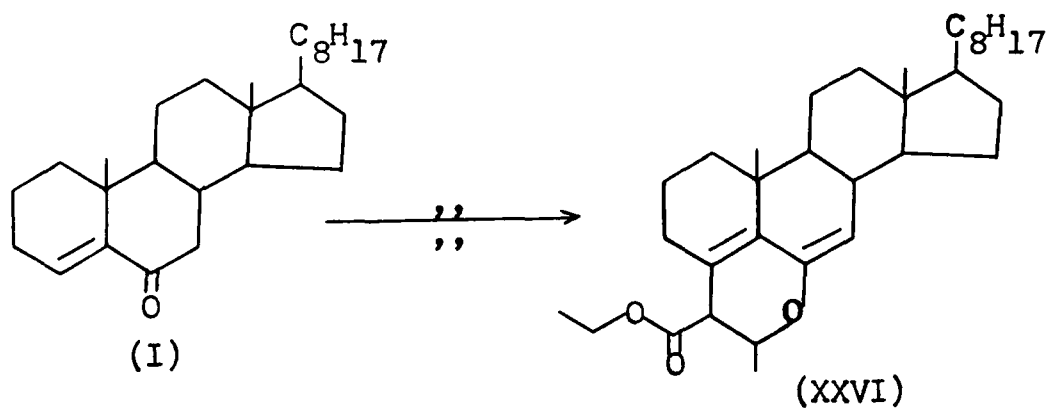
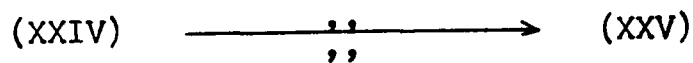
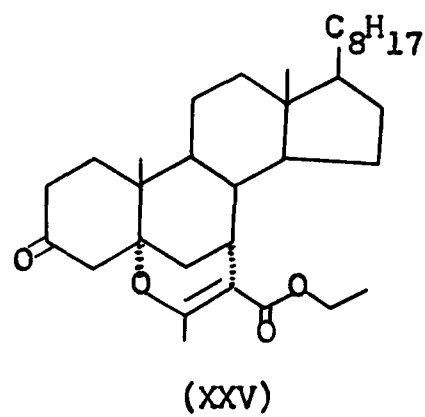
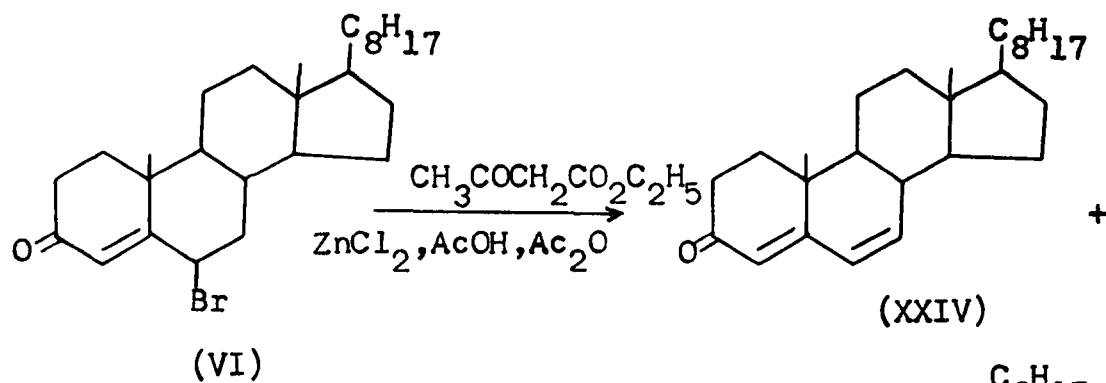
In order to assess the consistency of the reaction between steroidal α,β -unsaturated ketones and phenylhydrazine leading to pyrazoles, it was considered desirable to extend this study on to the stigmastane series. For this purpose 4-stigmasten-6-one (XVII), 6-oxo-4-stigmasten- 3β -yl acetate (XVIII) and 4-stigmastene-3,6-dione (XIX) were treated with phenylhydrazine. The results summarized below are consistent with the earlier observations made in the cholestane series.



STEROIDAL PYRANS

Compounds containing pyran, dihydropyran or pyrone moiety show high antiallergic, cytotoxicity and/or antitumor activity. Many workers reported the synthesis of pyrans by the reaction of α,β -unsaturated ketones and ethylacetoacetate. Survey of the literature revealed that applicability of these reactions to the steroidal substrates seems to be overlooked. Hence with a view of synthesizing pyrans in the steroidal systems we carried out the reactions of some of the easily accessible α,β -unsaturated ketones in the cholestane series with ethylacetoacetate in the presence of zinc chloride acetic acid and acetic anhydride. The following chart shows the reactions of the various α,β -unsaturated ketones (I, III, V, VI, XXIV and XXVII) with ethylacetoacetate.

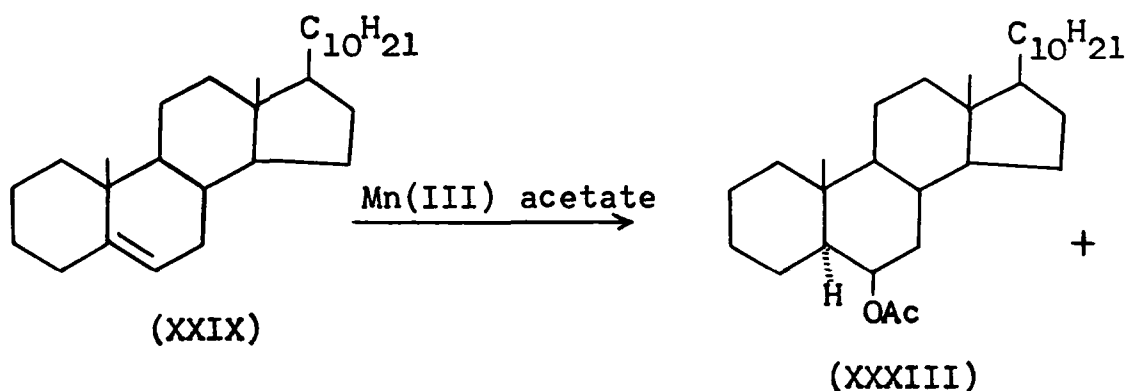


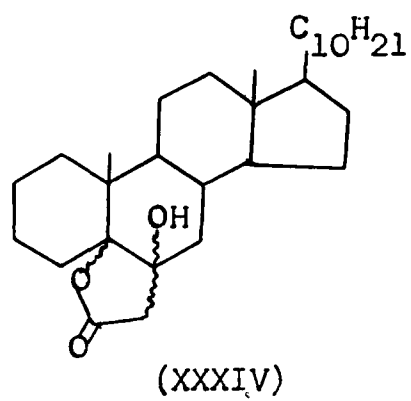


OXIDATION OF STEROIDAL OLEFINS WITH Mn(III) ACETATE

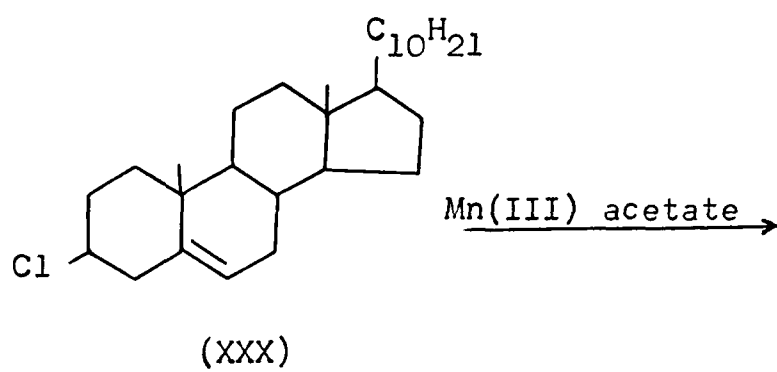
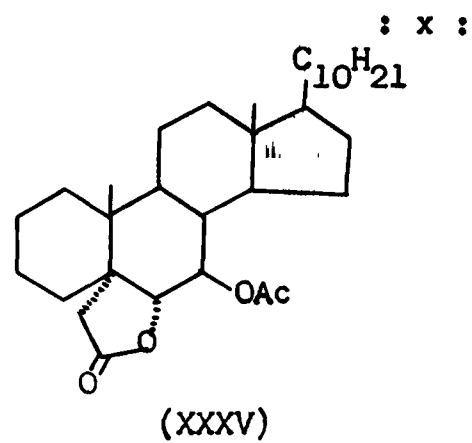
The oxidation of olefins with Mn(III) acetate has been studied extensively, which leads to the formation of γ -lactones alongwith other side products. Recently the synthesis of γ -lactones has attracted the attention of organic chemists for their potentialities as allergenic, growth inhibitor, antibacterial and antitumor activity. Reaction of Mn(III) acetate with steroidal olefins has remained by large unexplored.

Recently the formation of γ -lactones in the cholestane series has been reported from our laboratory by the oxidation with Mn(III) acetate in the presence of acetic acid and propionic acid. As an extension 5-stigmastene (XXIX), 5-stigmasten-3 β -yl chloride (XXX), 5-stigmasten-3 β -yl acetate (XXXI) and 5-stigmasten-3 β -yl propionate (XXXII) were subjected to the similar reaction conditions. The products obtained have been summarized in the following table.

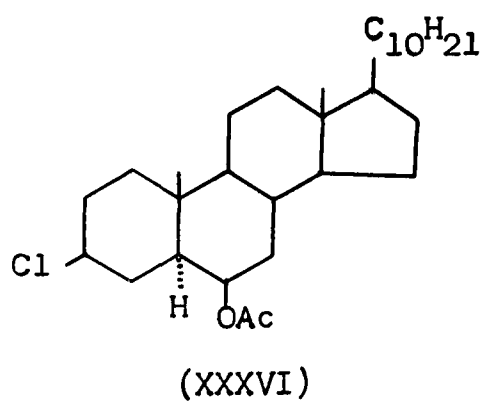




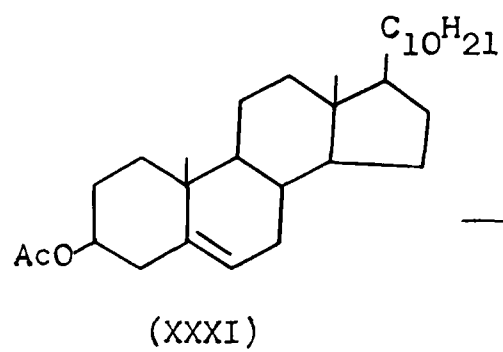
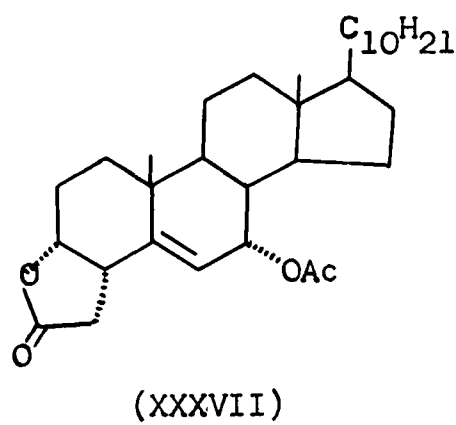
+



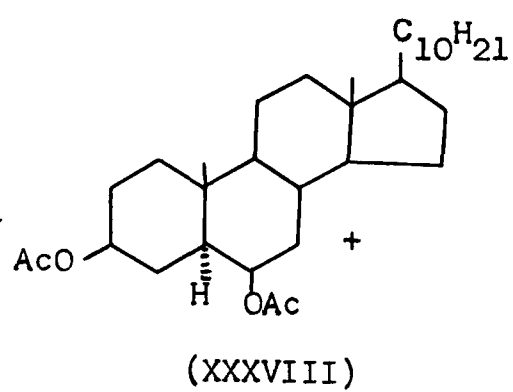
$\xrightarrow{\text{Mn(III) acetate}}$



+

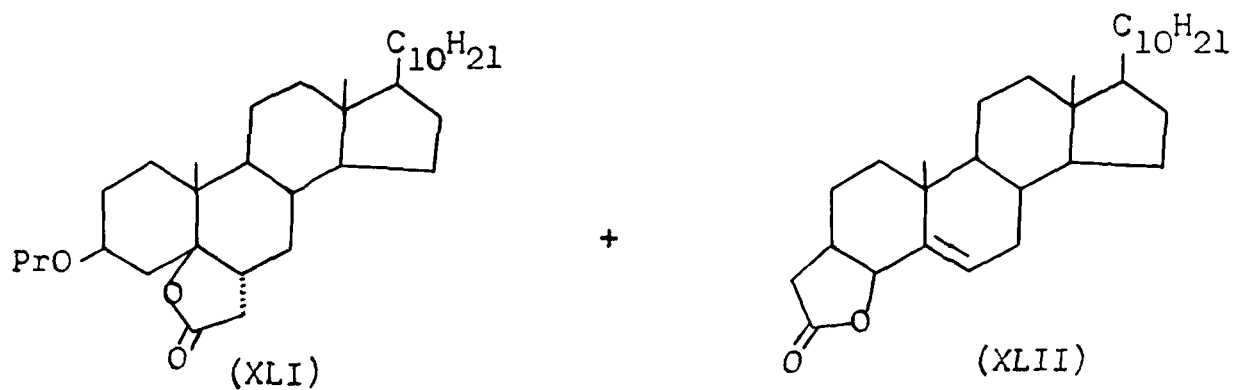
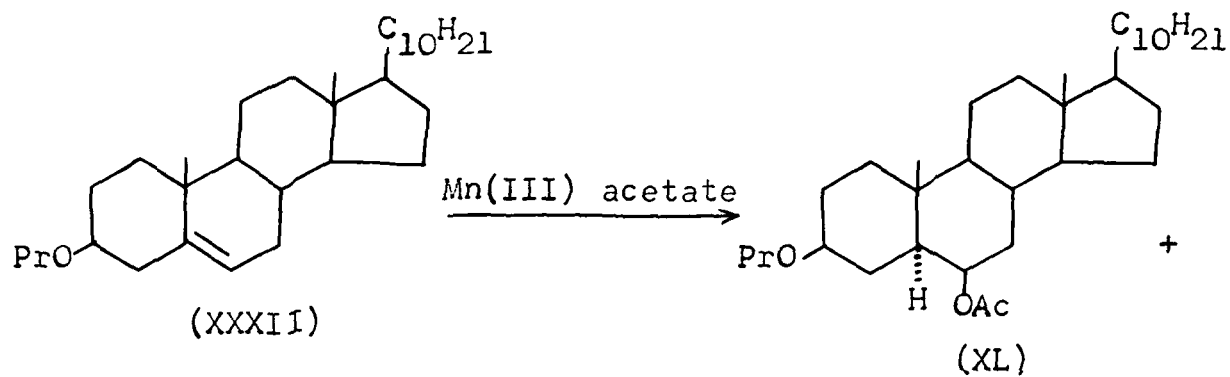
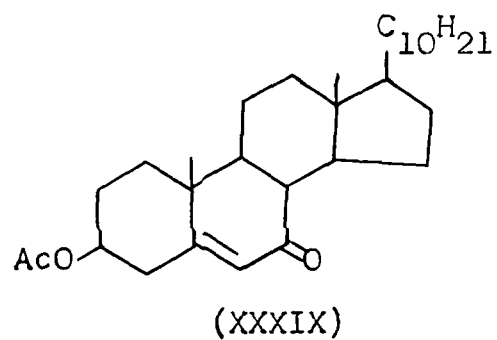


$\xrightarrow{\quad}$



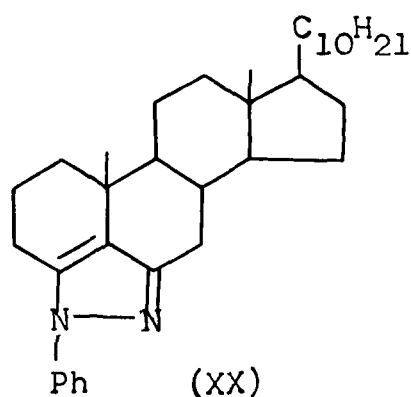
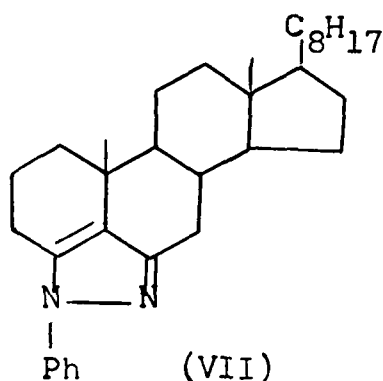
(XXXVII)

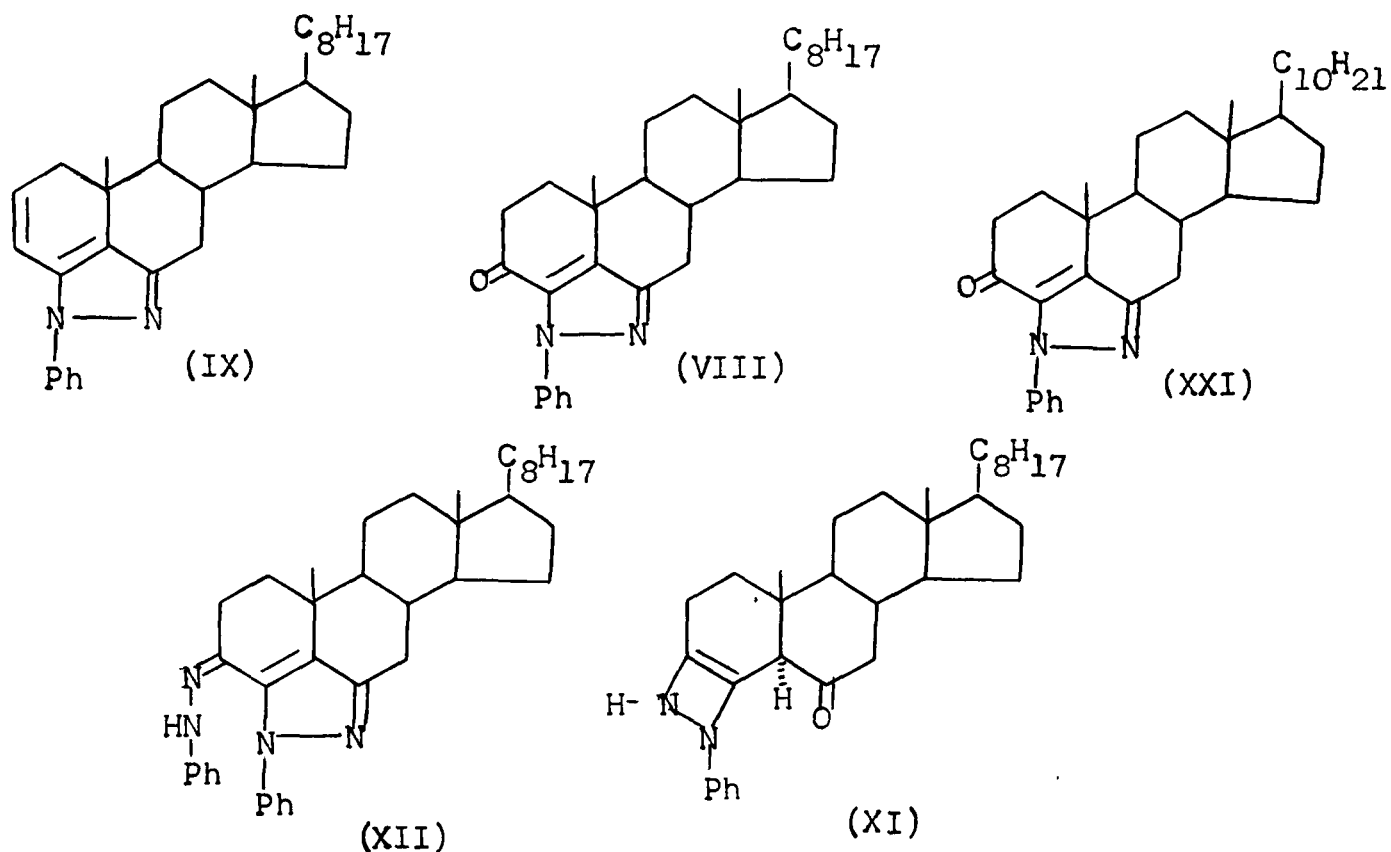
+



MASS SPECTRAL STUDIES ON STEROIDAL COMPOUNDS(a) Steroidal pyrazoles

A survey of the literature revealed that no systematic mass spectral study of steroidal pyrazoles has been reported. In the previous part we have described the preparation of a number of steroidal pyrazoles. These two events prompted us to examine the mass spectra of several structurally related steroidal pyrazoles. These include 2'-phenyl-4-cholesteno[4,6-cd]pyrazole (VII), 2'-phenyl-4-stigmasteno[4,6-cd]pyrazole (XX), 2'-phenyl-2,4-cholestadieno[4,6-cd]pyrazole (IX), 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]pyrazole (VIII), 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]pyrazole (XXI), 2'-phenyl-4-cholesteno[4,6-cd]pyrazole-3-one phenylhydrazone (XII) and 6-oxo-5 α -3-cholesteno[3,4]N,N-phenylhydrazine (XI). These compounds are structurally very close to each other. It was anticipated that they will follow similar fragmentation pattern thus offering a simple and effective method for their characterization by mass spectrometry.

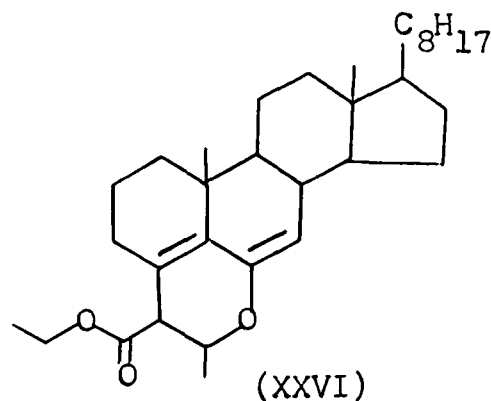
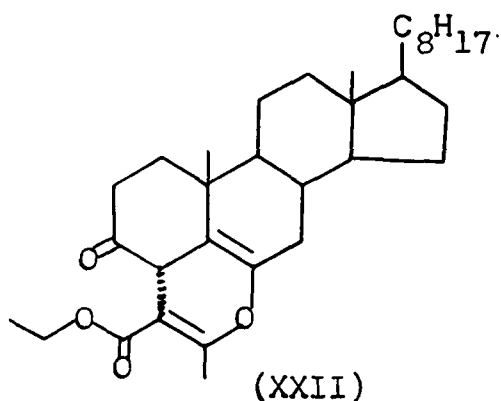




A comparison of mass spectra of pyrazoles (VII, XX, IX, VIII, XXI and XII) clearly showed remarkable similarity between them. These six pyrazoles represent changes in the different parts of the molecule which can be made use of in the interpretation of the spectra. Screening of these spectra revealed that these steroidal pyrazoles undergo characteristic fragmentation which can be exploited for identification purposes.

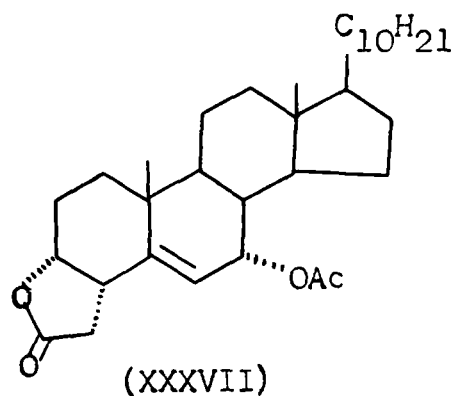
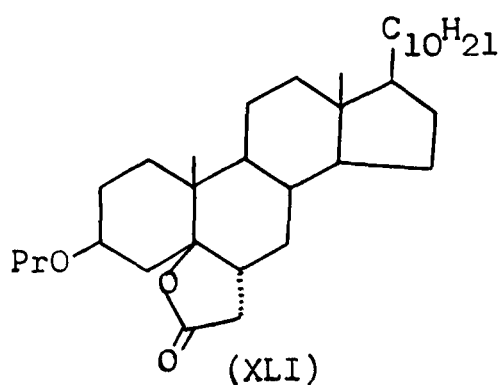
(b) Steroidal pyrans

A survey of the literature revealed that no mass spectral study of steroidal pyrans has been reported though mass spectra of several pyrans have been examined. The present chapter, as an initial chapter is concerned with a very limited number of steroidal pyrans such as 2'-methyl-3'-carboethoxy-3-oxo-5-cholesteno[4,6-de]- γ -pyran (XXII) and 2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydropyran (XXVI). Furthermore, these pyrans are not structurally very closely related to each other and therefore, their mass spectral study has very limited scope under the circumstances. Nevertheless we considered it necessary and interesting to look into the mass spectra of these compounds.



(c) Steroidal γ -lactones

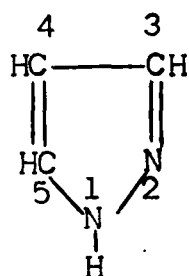
The concluding part of the chapter deals with the mass spectral study of two γ -lactones, belonging to the stigmastane series. They are 3β -propionoxy- 5β -hydroxystigmast- 6α -yl acetic acid γ -lactone (XLI) and 7α -acetoxy- 3α -hydroxystigmast- 5 -en- 4α -yl acetic acid γ -lactone (XXXVII). In an earlier work from our laboratory mass spectra of several γ -lactones belonging to the cholestane series have been examined. It may be pointed out that the main idea at present is to compare the spectra of the γ -lactones in the two series, namely the cholestane and the stigmastane series.



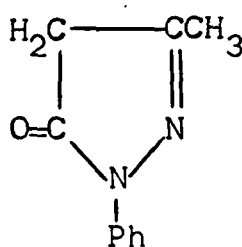
THEORETICAL

PYRAZOLES

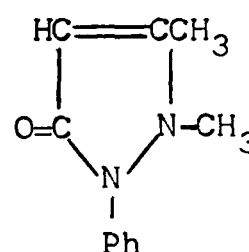
The pyrazole system (I) consists of a doubly unsaturated five membered ring containing two adjacent nitrogen atoms. Knorr^{1,2} first synthesized a compound containing this system in 1883 by the reaction of ethylacetoacetate with phenylhydrazine which yields 1-phenyl-3-methyl-5-pyrazolone (II). His interest in quinine led to tests of the antifebrile action of this and related compounds which resulted in the discovery of antipyrine³ (III), an important febrifuge.



(I)



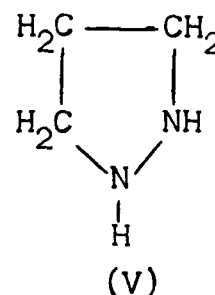
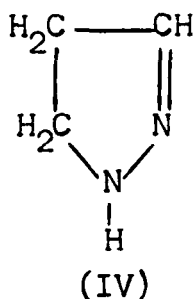
(II)



(III)

Knorr⁴ introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon by nitrogen; he synthesized many members of the class and systematically investigated their properties. Since many drugs and dyes contain pyrazole nucleus the class has been widely studied.

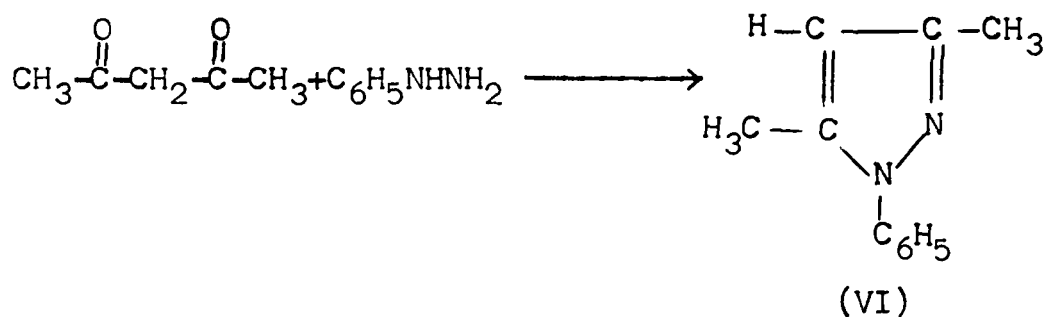
General heterocyclic nomenclature rules lead to the numbering shown in (I) for pyrazoles and the names pyrazoline and pyrazolidine for the dihydro and tetrahydropyrazoles (IV) and (V).



Three general methods have been used for the synthesis of pyrazoles and pyrazoline derivatives.

1. From hydrazine and 1,3-dicarbonyl compounds

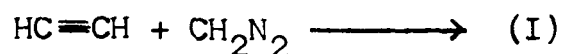
The reaction of a 1,3-dicarbonyl compound with hydrazine or substituted hydrazine to form pyrazole is a general reaction that commonly occurs under the ordinary conditions of hydrazone formation. Occasionally monohydrazones⁵ have been isolated and have sometimes been converted to the corresponding pyrazoles with acid or heat. Bishydrazones^{6,7} have also been reported and in a few instances have been converted to pyrazoles similarly⁶.



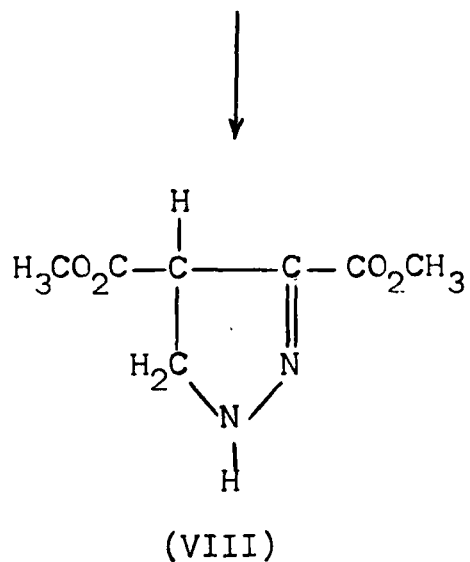
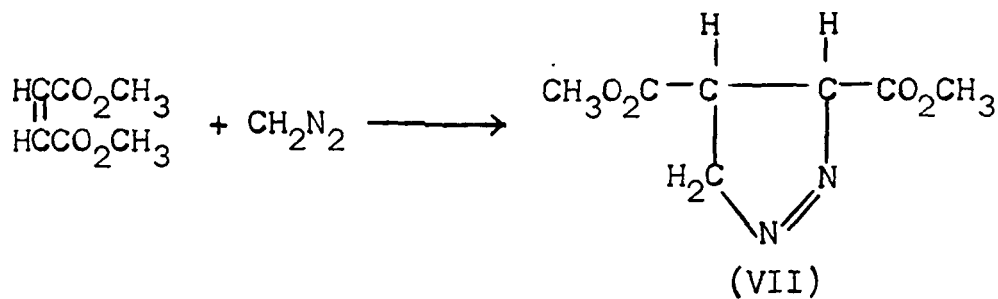
The synthesis of pyrazolones from β -ketoester is analogous.



2. From the reaction of aliphatic diazo compounds such as diazomethane or diazoacetic ester with acetylenes or olefins.



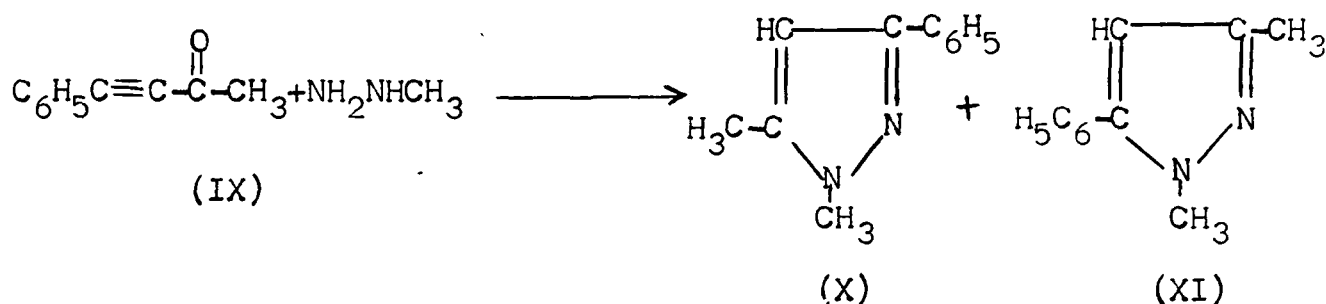
Pyrazolines are readily obtained from α,β -unsaturated esters and diazo compounds⁸.



The Δ^+ -pyrazoline (VII), that is formed first as a rule, rearranges spontaneously to Δ^2 -compound (VIII), as this results in the formation of a conjugated system.

3. From α,β -unsaturated carbonyl compounds

The synthesis of pyrazoles by the reaction of α,β -acetylenic carbonyl compounds with hydrazine and its derivatives is less common than the corresponding pyrazoline synthesis from α,β -ethylenic carbonyl compounds because the acetylenic compounds are less readily available and the reaction is somewhat difficult. The pyrazole synthesis is generally successful when hydrazine is used and a hydrazone is seldom isolated⁹. It might be assumed that a hydrazone is an intermediate in this synthesis.



This need not be true, because the addition of amines to the triple bond of α,β -acetylenic carbonyl compounds is well known^{10,11}, and addition of the hydrazine in a similar manner may

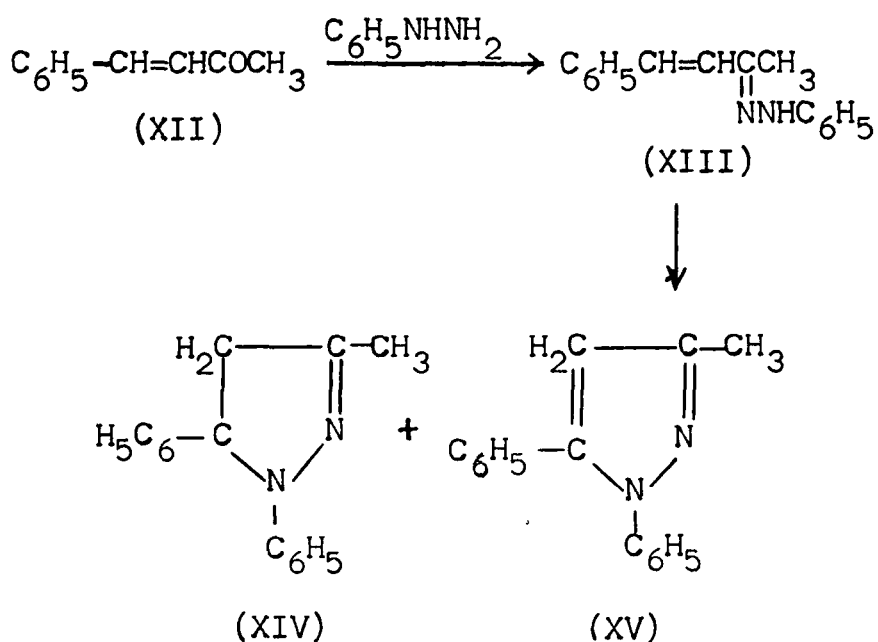
be the first step in the reaction. 1-Phenyl-1-butyne-3-one (IX) and methylhydrazine gives both (X) and (XI). In other cases the only compound isolated appears to have the structure predicted from ring closure of the hydrazone^{9,12}.

The most general method for pyrazoline synthesis is the reaction of hydrazine with α,β -unsaturated aldehydes and ketones. Phenylhydrazones can be isolated in many instances with phenylhydrazine and these intermediates generally rearrange to pyrazoline on refluxing in acetic acid. Purely aliphatic α,β -unsaturated aldehydes, such as crotonaldehyde and α -methylacraldehyde, yielded phenylhydrazones which resinify in air and are not converted to pyrazolines with acetic acid^{13,14}. However, in hot aqueous sodium hydroxide these two aldehydes react with phenylhydrazine to give moderate yield of pyrazoline. Acrolein gives both a phenylhydrazone and 1-phenylpyrazoline¹³. Pyrazolines are obtained directly from aliphatic α,β -unsaturated ketones, such as mesityloxide, although 3-decen-2-one was reported to yield a phenyl hydrazone¹³.

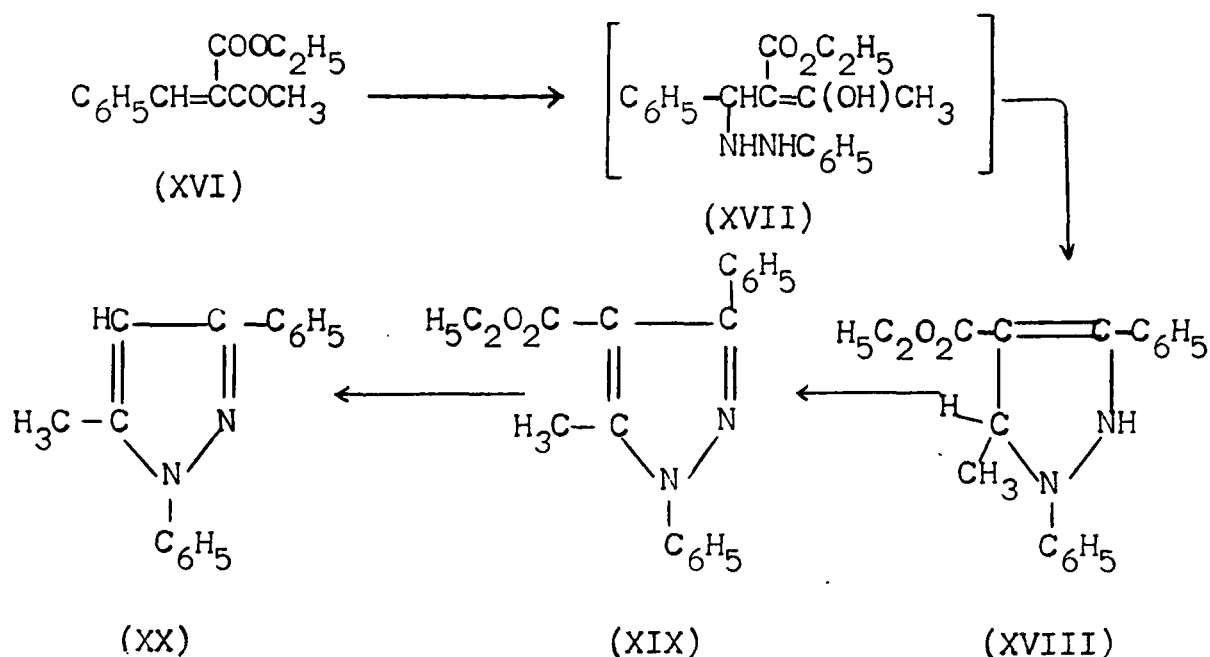
The presence of electron-releasing groups such as hydroxyl, alkoxyl and amino on either phenyl group of benzalacetophenone makes the phenylhydrazone more labile, and it can seldom be isolated^{15,16}; electron withdrawing groups such as nitro and halogen stabilize the intermediate¹⁵⁻¹⁸. In most of these studies the phenylhydrazones were obtained at room temperature in acetic

acid or in alcohol containing a little acetic acid. Further studies on the effect of various substituents in the aryl group on pyrazoline formation were made with unsymmetrically substituted dibenzalacetones, $\text{XC}_6\text{H}_4\text{CH}=\text{CHCOCH}=\text{CHC}_6\text{H}_4\text{Y}$ ^{17,19}. Ring closure occurs in the direction of a phenyl group containing an alkoxy or dimethylamino group more readily than towards an unsubstituted phenyl group, and towards the latter in preference to the direction of a nitro or halo-phenyl.

It might be expected that the reaction of an α,β -unsaturated carbonyl compound with phenylhydrazine or other substituted hydrazines would proceed through hydrazone formation and ring closure in a straightforward way to give a pyrazoline of known structure. This has been shown to be the course of the reaction with benzalacetone²⁰ (XII-XV), phenylpropyl ketone²⁰, cinnamaldehyde^{21,22} phenylvinyl ketone²³ and a few other compounds.



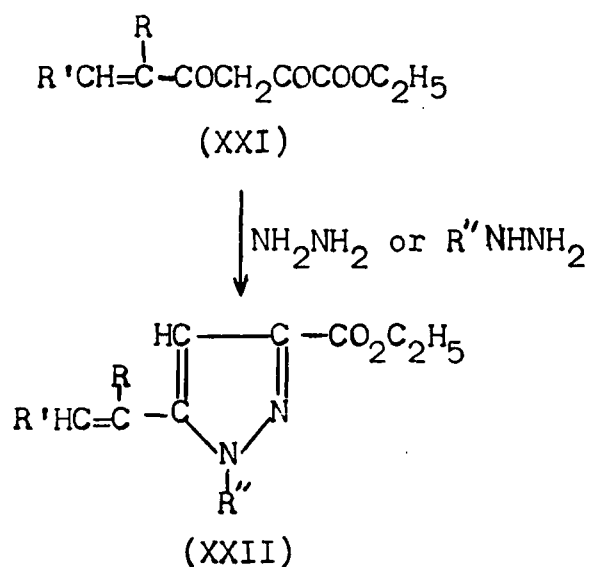
Benzalacetone with phenylhydrazine yields benzalacetone phenylhydrazone (XIII), which on cyclization gives pyrazoline (XIV) and pyrazole (XV). However, an alternative course for the reaction appears to be possible, although rare. Benzalacetoacetic ester (XVI) reacts in cold with phenylhydrazine to give ethyl-1,3-diphenyl-5-methylpyrazole-4-carboxylate (XIX) which is readily saponified and decarboxylated to yield 1,3-diphenyl-5-methylpyrazole²⁰ (XX). This reaction is abnormal in other ways; no pyrazoline is isolated and the pyrazole is obtained in high yield even when the reaction is carried out in an inert atmosphere.



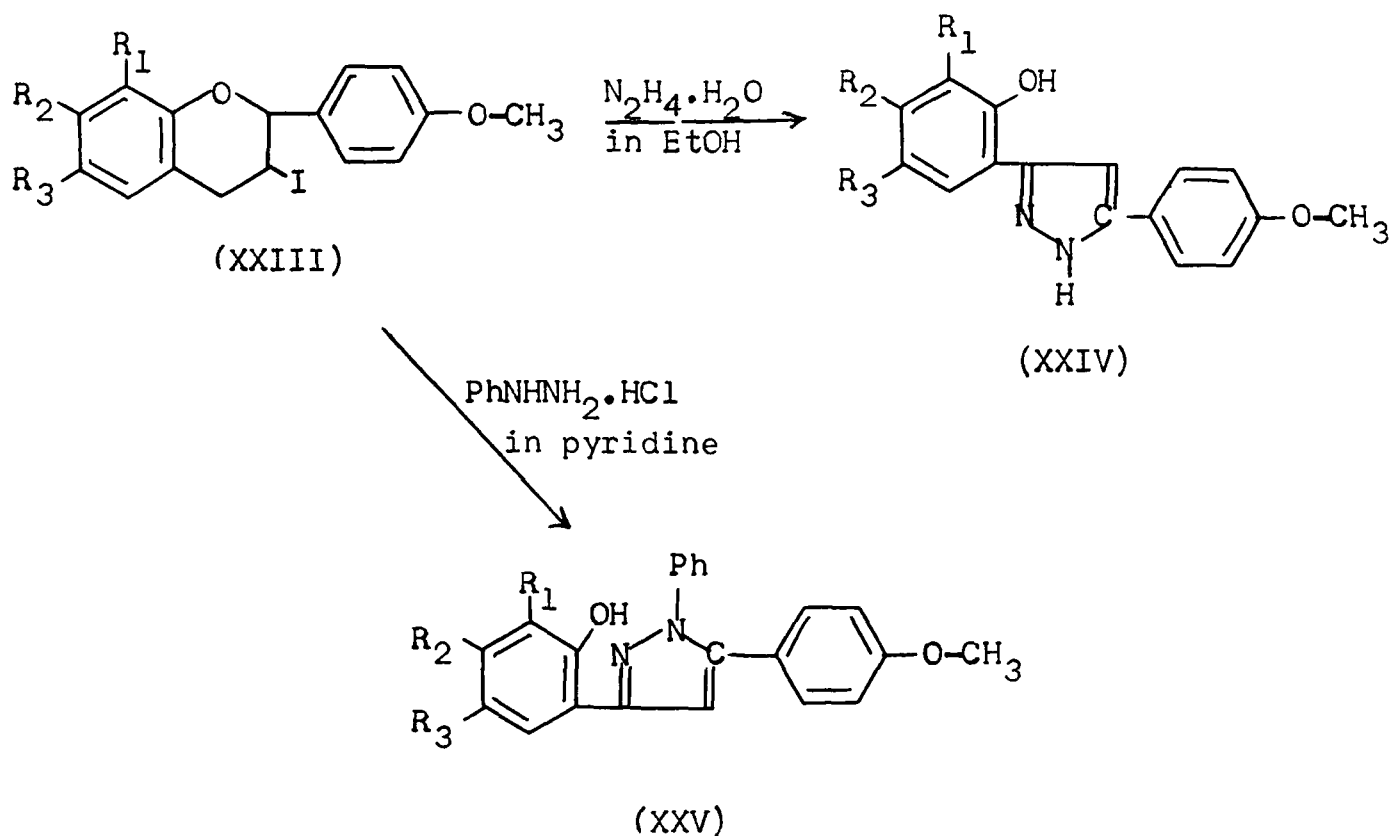
No evidence for intermediates (XVII) and (XVIII) was given, but Auwers²² speculated that loss of hydrogen to yield a pyrazole spontaneously was a property of Δ^3 -pyrazolines such as

(XVIII). The dehydrogenation of pyrazoline to a pyrazole in the absence of oxidizing agents²⁴ or during formation from a phenylhydrazine such as (XIII) which gives both (XIV) and (XV) when heated²⁵, is encountered occasionally²⁶.

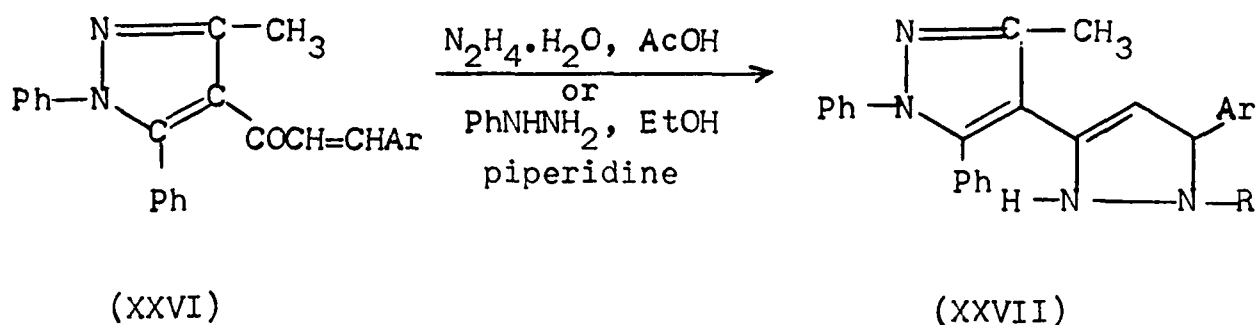
Mokhtar and Wajtanis²⁷ reported the synthesis of pyrazole by the reaction of ethyl-6-substituted-5H-substituted-2,4-dioxo- Δ^5 -hexenoates (XXI) with hydrazine and arylhydrazine which afforded corresponding ethyl-1-H-substituted-5-substituted pyrazole-3-carboxylates (XXII).



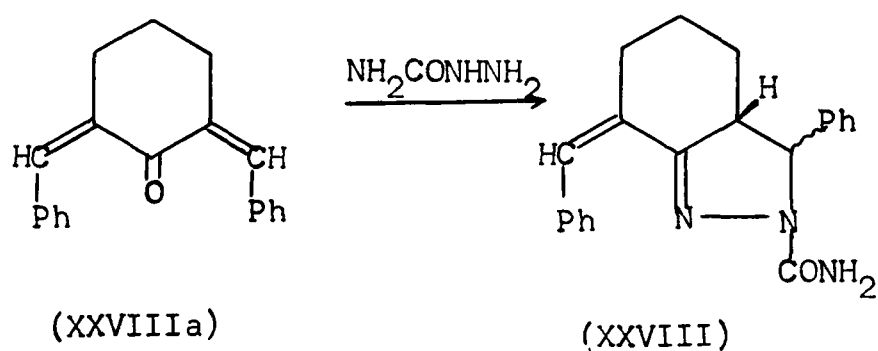
Joshi et al.²⁸ in 1981 isolated 3,5-diaryl pyrazole (XXIV) from the reaction of 3-indoflavones (XXIII) with hydrazine in ethanol at room temperature and 3,5-diaryl-1-phenyl pyrazole (XXV) from the reaction of (XXIII) with phenylhydrazine in pyridine.



Hammouda and Hussain²⁹ reported the synthesis of pyrazoles by cyclocondensation of 4-cinnamoyl-1,5-diphenyl-3-methylpyrazole (XXVI) with hydrazine hydrate in acetic acid and phenylhydrazine in ethanol in the presence of piperidine. They obtained the corresponding pyrazoliny pyrazole (XXVII); the structure of which was established by elemental analysis, IR, PMR and colour test characteristic of arylpyrazolines^{30,31}.

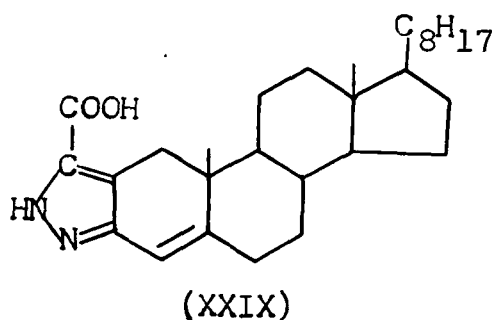


Szabo et al.³² prepared a series of bi- and tricyclo 4,5-dihydropyrazoles by the treatment of mono- and dibenzylidene cycloalkanones with aminourea or aminothiurea e.g. treatment of 2,5-dibenzylidene cyclohexanone (XXVIIIa) with aminourea in refluxing ethanol containing hydrochloric acid for two hours gave a mixture of (XXVIII) (3α -Ph and 3β -Ph).



Steroidal pyrazoles

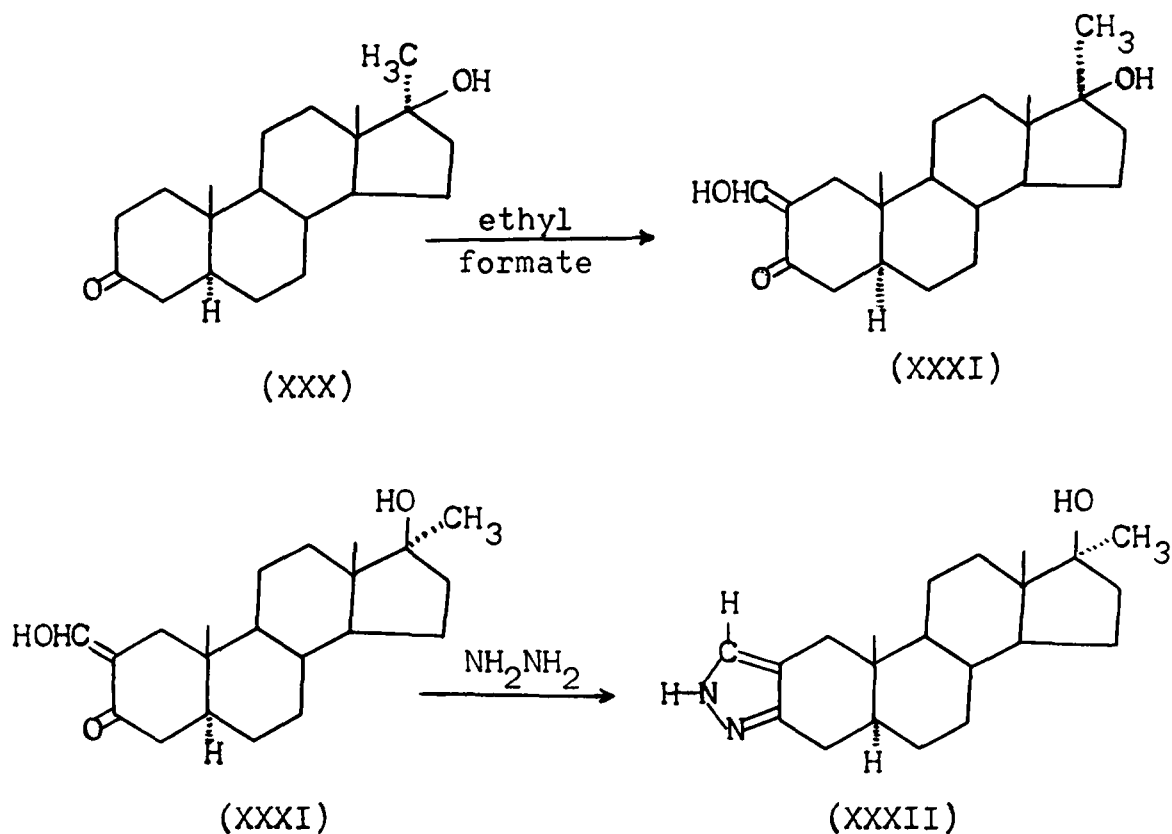
Perhaps the first steroidal pyrazole was synthesized by Ruzicka³³ in 1938. He reported the formation of a single compound cholest-4-eno[3,2-c]pyrazole-5'-carboxylic acid (XXIX).



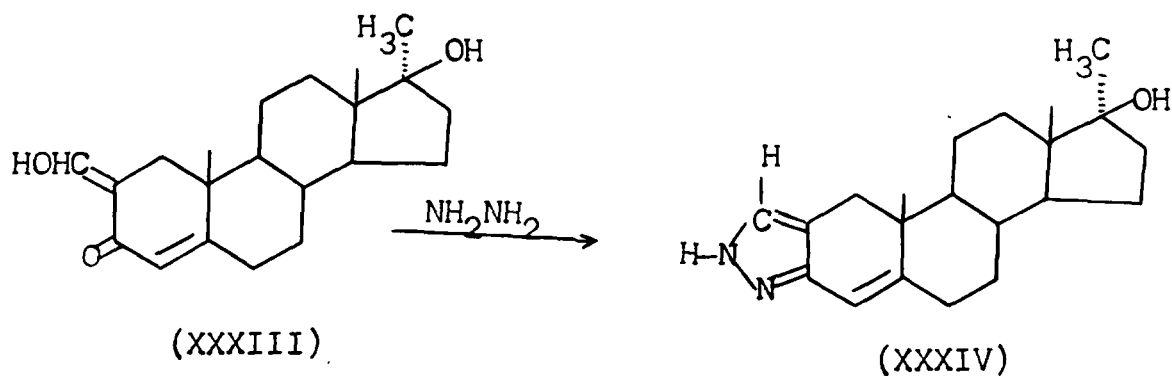
After a considerable span of time much attention has been given by a number of organic chemists towards the synthesis of steroidal pyrazoles. The biological activities associated with them motivated organic chemists towards their synthesis. Steroidal pyrazoles were found to effect on endocrinological activity³⁴⁻³⁷ and this observation prompted the investigations.

Clinton et al.³⁴ in 1959 found that steroidal [3,2-c] pyrazoles constitute a novel series of compounds with considerable endocrinological interest. Several of these compounds show remarkable separation or change in pattern of hormonal activity when compared to parent steroids.

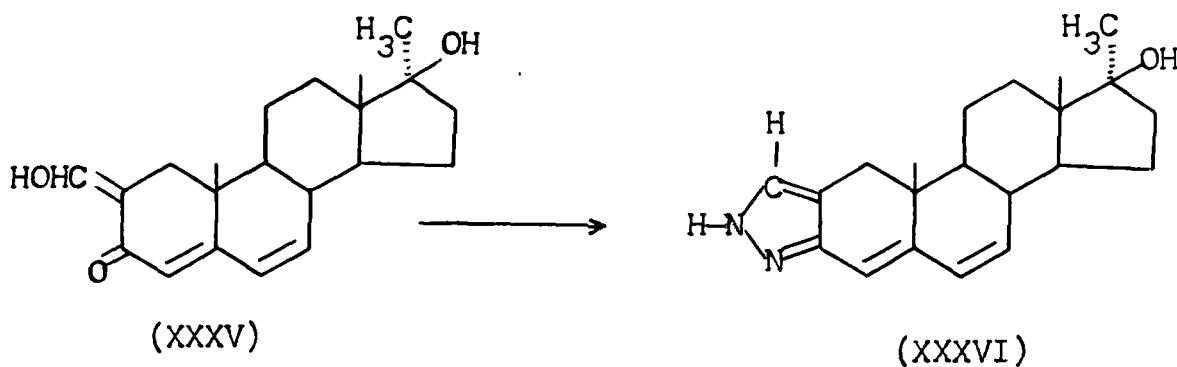
Treatment³⁴ of 17 α -methylandrostan-17 β -ol-3-one (XXX) with ethylformate and sodium methoxide gave 2-hydroxymethylene derivative (XXXI) which on condensation with hydrazine gave 17 β -hydroxy-17 α -methylandrostano[3,2-c]-pyrazole (XXXII).



Treatment of 2-hydroxymethylene-17 α -methylandrost-4-en-17 β -ol-3-one (XXXIII) with hydrazine gave 17 β -hydroxy-17 α -methyl-androst-4-eno[3,2-c]-pyrazole (XXXIV)³⁴.



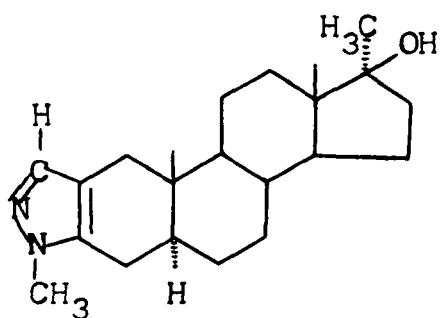
Similar treatment of (XXXV) with hydrazine afforded homologous 17 β -hydroxy-17 α -methylandrosta-4,6-dieno[3,2-c]-pyrazole (XXXVI)³⁴.



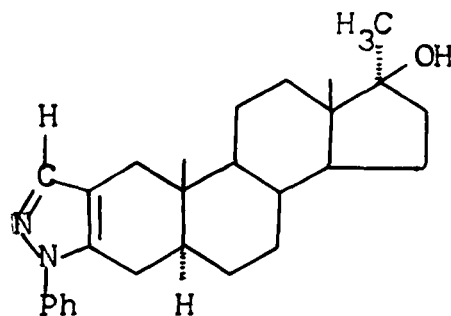
The unusual activity observed with the above compounds has led to the preparation of steroidal pyrazoles related to the progestational and cortical hormones as well as to the fusion of steroids with other heterocyclic rings. Some of the simple 2-hydroxymethylene-3-keto-17 α -alkylandrostanes and their Δ^4 - analogues have a fair to good degree of oral anabolic activity.

But in all cases the anabolic activities of 2-hydroxymethylene-3-keto steroids were less interesting than those of their steroidal [3,2-c]-pyrazoles. 2-Hydroxymethylene-17 α -methylandrostan-17 β -ol-3-one (XXXI) had shown oral anabolic activity in humans³⁵.

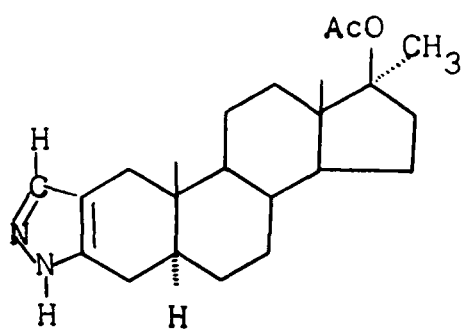
Clinton et al. in 1961³⁶ utilizing a new approach to the concept of altering the structure-activity relationship in anabolic steroids, synthesized several type of steroidal[3,2-c]-pyrazoles. They reported the formation of 17 β -hydroxy-17 α -methylandrostano [3,2-c]-2'-methylpyrazole (XXXVII), 17 β -hydroxy-17 α -methylandrostano [3,2-c]-2'-phenylpyrazole (XXXVIII), 17 β -acetoxy-17 α -methylandrostano [3,2-c]-pyrazole (XXXIX), 17 β -hydroxyandrost-4-eno[3,2-c]-pyrazole (XL), 17-ketoandrost-4-eno[3,2-c]-pyrazole (XLI), 17 β -hydroxy-17 α -methyl-19-norandrost-4-eno[3,2-c]-pyrazole (XLII) and 17 β -hydroxy-17 α -methylandrosta-4,6-dieno[3,2-c]-pyrazole (XXXVI), from their corresponding-2-hydroxymethylene-3-ketoandrostanes.



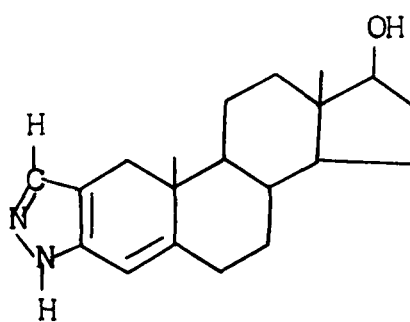
(XXXVII)



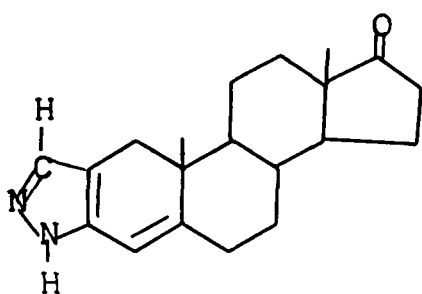
(XXXVIII)



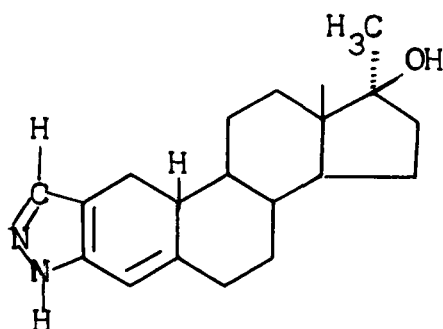
(XXXIX)



(XL)



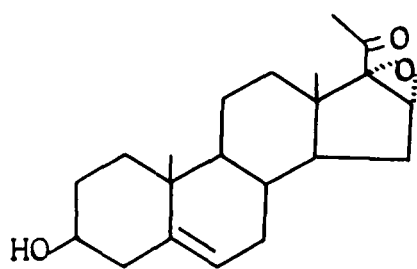
(XLI)



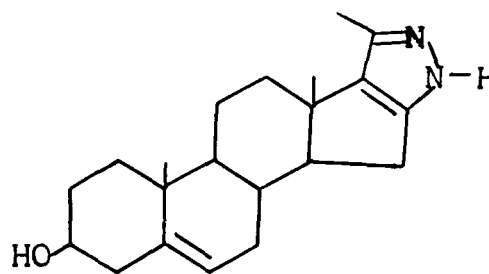
(XLII)

Studies revealed that androstan-17 β -ol-3-one and 17 α -methylandrostan-17 β -ol-3-one are highly anabolic and androgenic. The corresponding 17 β -hydroxyandrostan[3,2-c]-pyrazole and 17 β -hydroxy-17 α -methylandrostan[3,2-c]-pyrazole, on the other hand afforded a much greater separation of activities. The relative potency ratios for anabolic/androgenic activity are eight and one hundred twenty, respectively. The most conspicuous effect of the [3,2-c]-pyrazole moiety on endocrinological activity was observed when substitutions were made on the steroid nucleus in the androstano and androst-4-eno[3,2-c]-pyrazoles.

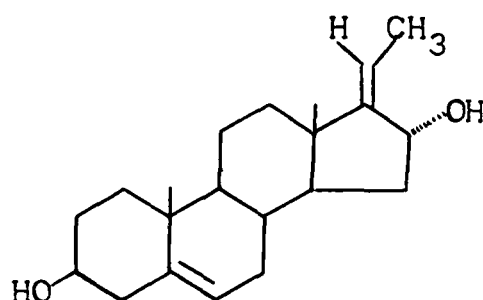
Benn and Dodson³⁷ obtained 3 β -hydroxyandrost-5-eno [16,17-c]-5'-methylpyrazole (XLIV) alongwith the two isomeric alcohols, 5,17(20)-(cis)-pregnadiene-3 β ,16 α -diol (XLV) and 5,17(20)-(trans)-pregnadiene-3 β ,16 α -diol (XLVI) when they carried out the hydrazine reduction of 16 α ,17-epoxypregnenolone (XLIII).



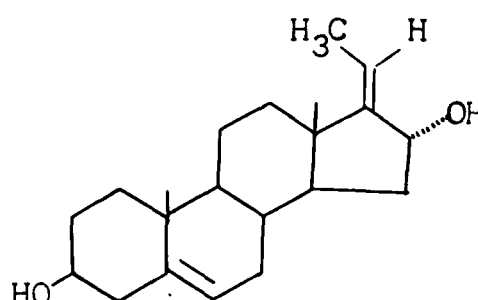
(XLIII)



(XLIV)



(XLV)



(XLVI)

Hirschmann and co-workers³⁸ reported the preparation of several [3,2-c]-pyrazoles related to cortisol, 16 α -methylcortisol and 4,5 α -dihydrocortisol. Their novel observation was that the pyrazoles are active as such and not because of the carbonyl

function at C₃ as observed by others^{34,39}. They described the synthesis of 5 α -pregnano and pregn-4-eno[3,2-c]-pyrazoles, related to cortisol and reported their biological activity. It was found that N-substituted and N-alkylated pyrazoles displayed biological activity of the same order as the parent steroid. Even more surprising was the observation that 2'-phenyl and specially the 2'-p-fluorophenyl derivatives are in fact the most powerful activity-enhancing functions so far observed in the antiinflammatory area.

The compound (XLIX) was prepared³⁸ from (XLVII) after protecting the side chain and then treating (XLVIII) with ethyl-formate in benzene. The compound (XLIX) when subjected to condensation with hydrazine, phenylhydrazine, N-substituted and N-alkylated hydrazines yielded [3,2-c]-pyrazoles (L-LX). The results have been given in Charts 1 and 2.

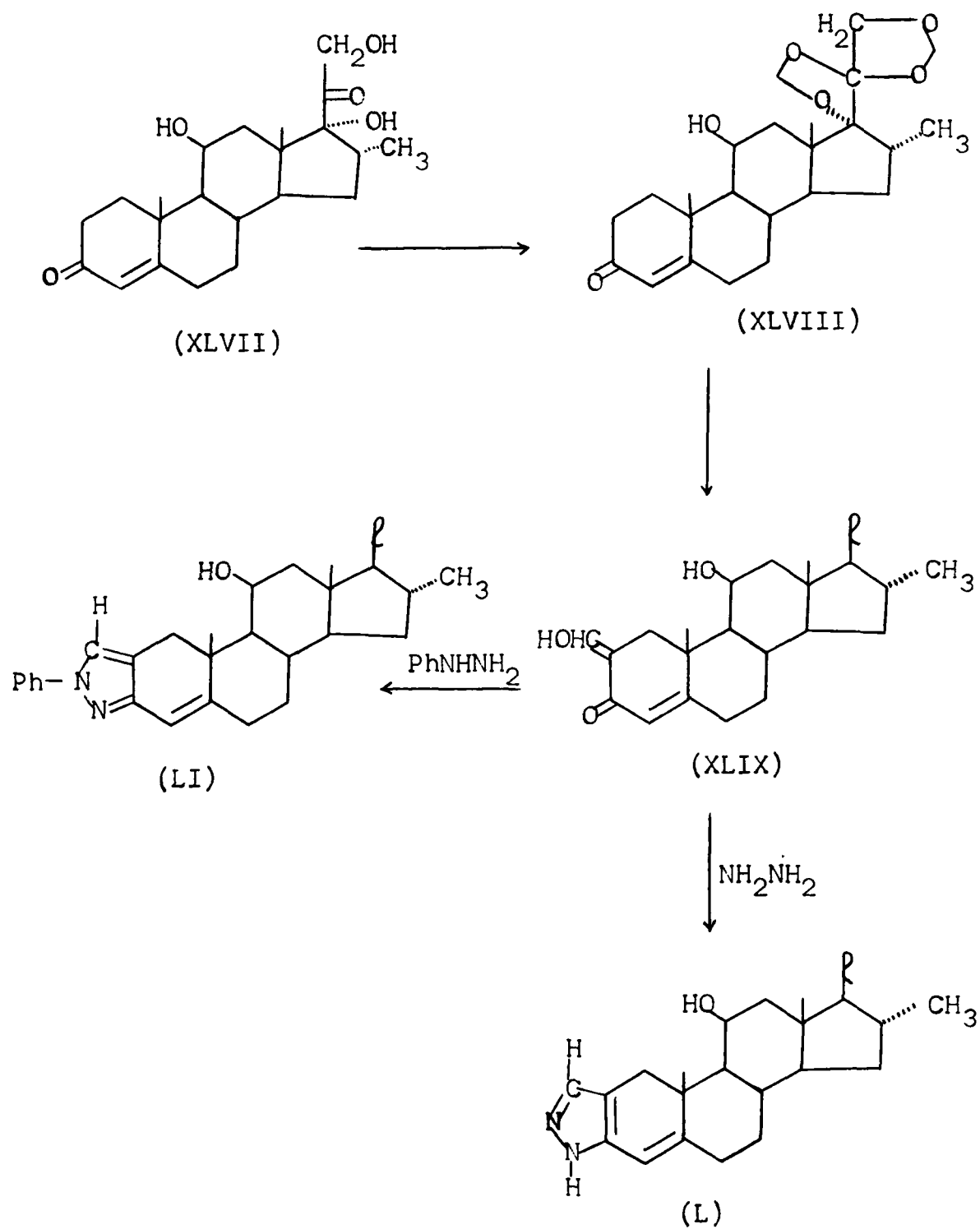
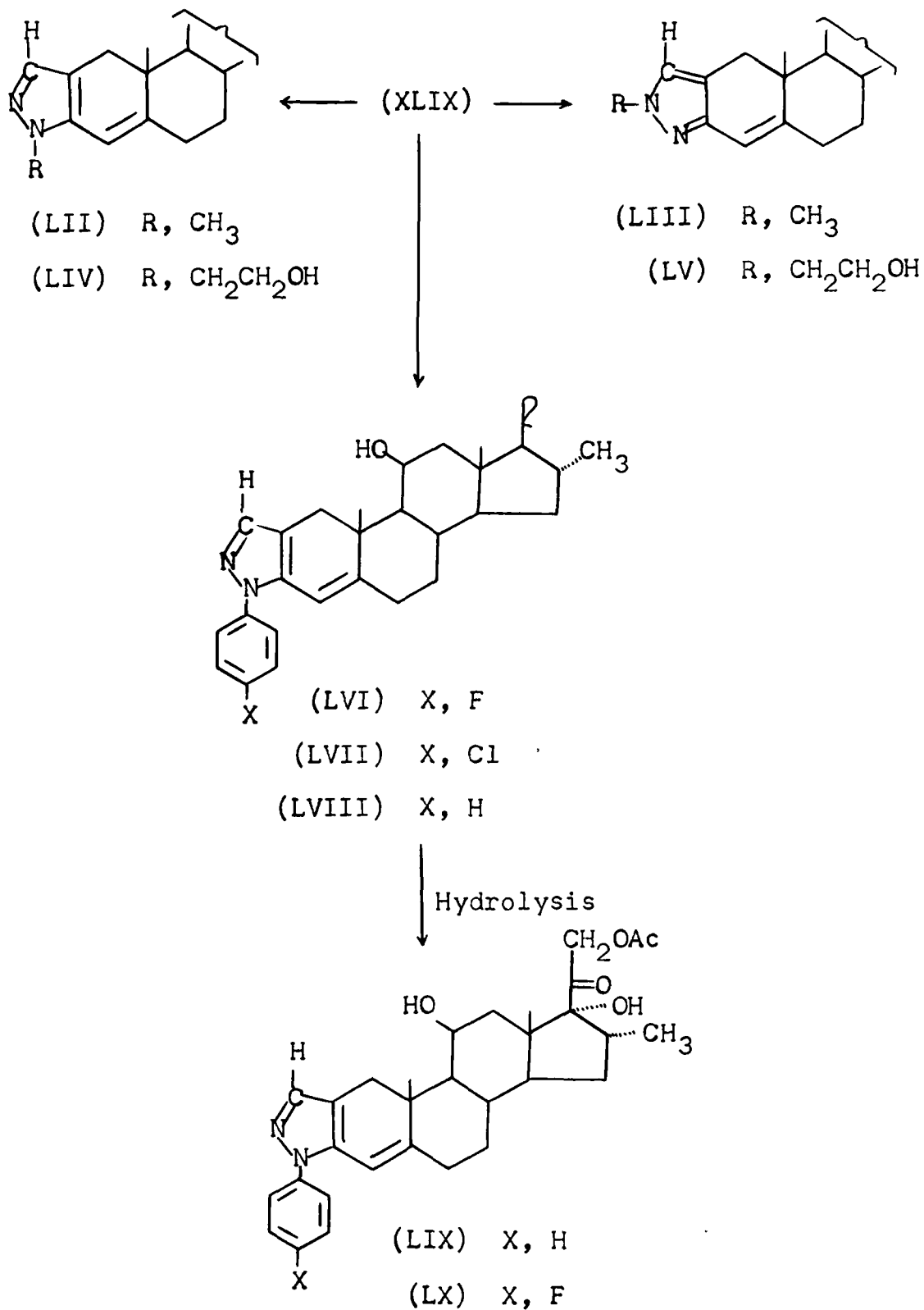
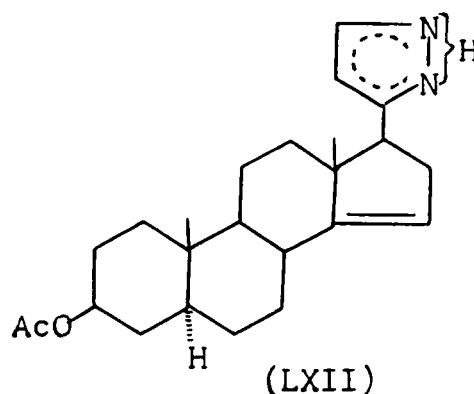
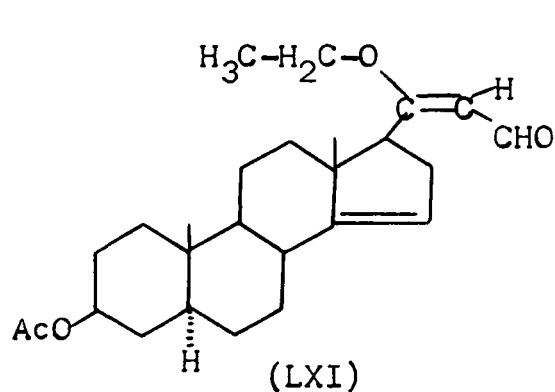
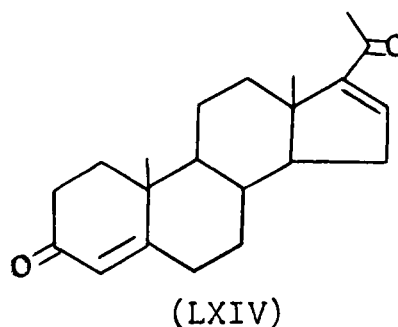
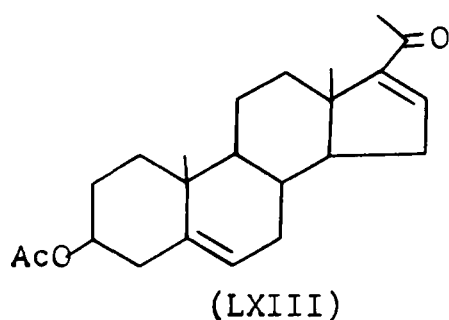
Chart - 1

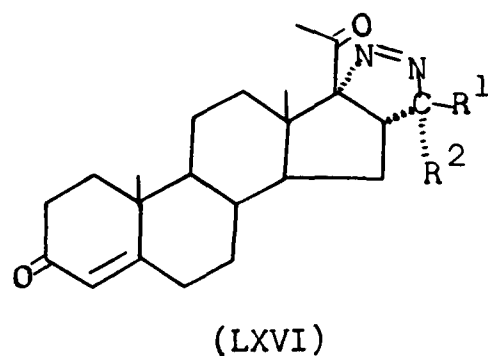
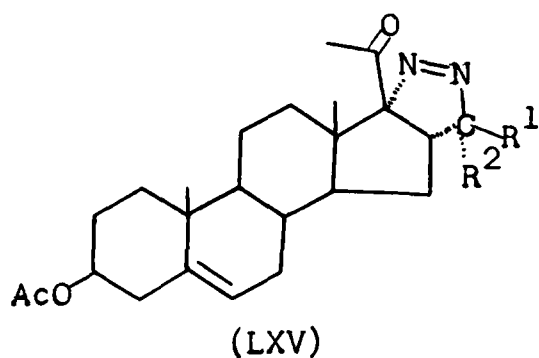
Chart - 2

Nambara et al.⁴⁰ in 1970 reported that the reaction of 20-ethoxy-21-formyl-17 β -pregna-14,20-diene (LXI) with hydrazine hydrate furnished 17 β -(3-pyrazolyl)-3 β -acetoxy-5 α -androsta-14-ene (LXII).



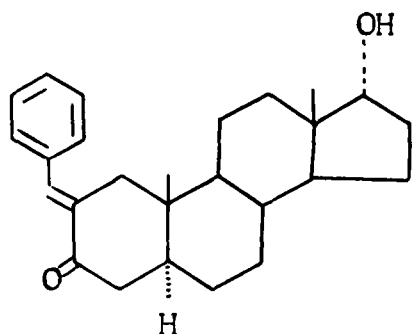
Bladon et al.^{41,42} carried out the reactions of a series of aliphatic diazocompounds with Δ^{16} -20-oxo-steroids which afforded the corresponding 4',5'-dihydro[17 α ,16 α -c]-pyrazoles-([17 α ,16 α -c]-pyrazolines). When diazocompounds (diazopropene, diazopropyne, 2-diazopropane and diazocyclopropane) were allowed to react with 3 β -acetoxypregna-5,16-diene-20-one (LXIII) and pregna-4,16-diene-3,20-dione (LXIV), they furnished the [17 α ,16 α -c]-pyrazolines (LXVa-e) and (LXVIa-e), respectively.



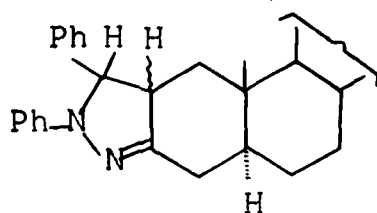


\underline{R}^1	\underline{R}^2	\underline{R}^1	\underline{R}^2
a. $-\text{CH}=\text{CH}_2$	H	a. $-\text{CH}=\text{CH}_2$	H
b. H	$-\text{CH}=\text{CH}_2$	b. $-\text{C}\equiv\text{CH}$	H
c. $-\text{C}\equiv\text{CH}$	H	c. Me	Me
d. Me	Me	d. $-\text{CH}_2-\text{CH}_2-$	$-\text{CH}_2-\text{CH}_2-$
e. $-\text{CH}_2-\text{CH}_2-$	$-\text{CH}_2-\text{CH}_2-$	e. H	$-\text{C}\equiv\text{CH}$

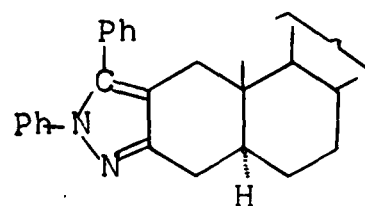
Synthesis of steroidal pyrazoles has also been reported⁴³ by cyclocondensation of benzylidene androstanone (LXVII) with phenylhydrazine. It afforded 2 α -(LXVIII) and 2 β -(LXVIII) which on dehydrogenation gave the pyrazole (LXVIIIa).



(LXVII)

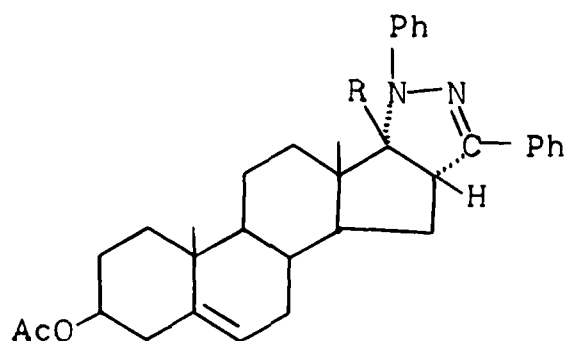
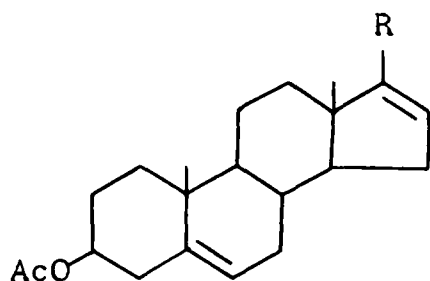


(LXVIII)



(LXVIIIa)

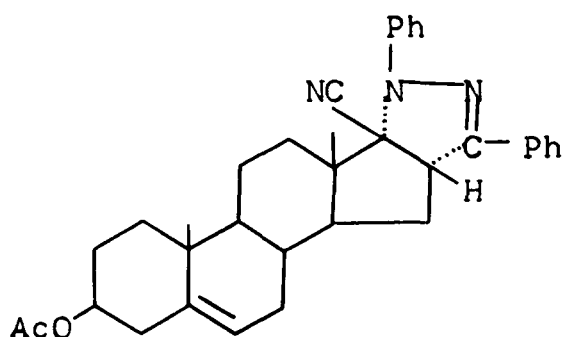
Green et al.⁴⁴ in 1978 reported the synthesis of several steroidal pyrazoles and pyrazolines in the androstane series. The addition of triethylamine to a mixture of the compound (LXIII) and benzoyl chloride phenylhydrazone, led to the formation of 3 β -acetoxypregna-5-en-20-ono[16 α ,17 α -d]-1',3'-diphenyl-2'-pyrazoline (LXIX) in 65% yield.



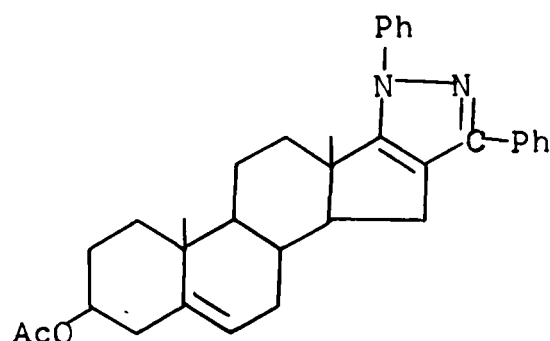
- (LXIII) R, COCH₃
 (LXX) R, COC₆H₅
 (LXXII) R, CN

- (LXIX) R, COCH₃
 (LXXI) R, COC₆H₅
 (LXXIII) R, CN

Diphenylnitrilimine⁴⁴ also added readily to the phenyl ketone (LXX) which gave bright yellow adduct (LXXI). Addition of diphenylnitrilimine to 3 β -acetoxy-17-cyanoandrosta-5,16-diene (LXXII) took place in the same regiochemical sense to yield 3 β -acetoxy-17 β -cyanoandrost-5-eno[16 α ,17 α -d]-1',3'-diphenyl-2'-pyrazoline (LXXIII). The pyrolysis of (LXXIII) at 290° resulted in the formation of 3 β -acetoxyandrost-5-eno[16,17-d]-1',3'-diphenyl pyrazole (LXXIV).

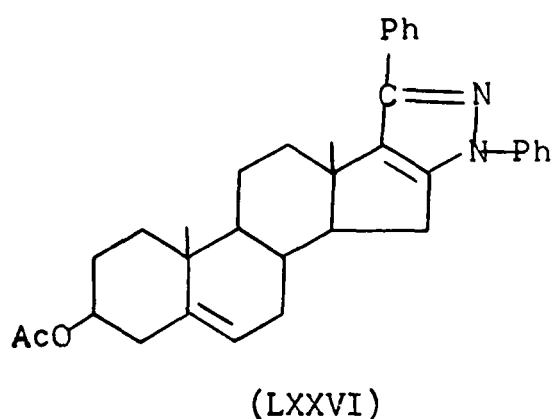
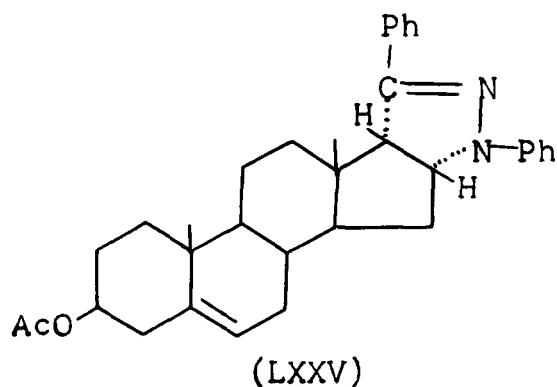
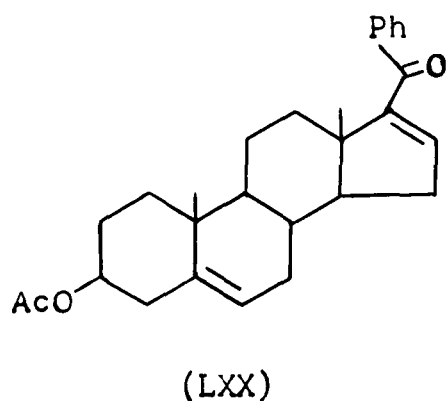


(LXXIII)

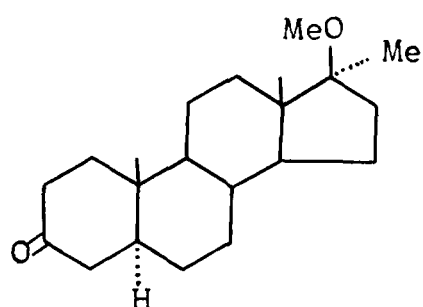


(LXXIV)

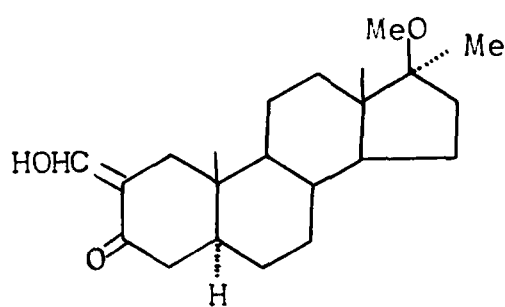
To confirm the regiochemistry of pyrazole (LXXIV) its regioisomer was prepared by converting (LXX) to its phenylhydrazone, followed by cyclization with ethanolic HCl to the diphenylpyrazoline (LXXV) which was dehydrogenated with dichlorodicyanobenzoquinone to 3 β -acetoxyandrost-5-ene[17,16-d]-1',3'-diphenylpyrazole (LXXVI). The pyrazole (LXXVI) was different markedly in m.p., i.r., n.m.r., u.v. and o.r.d. with that of (LXXIV).



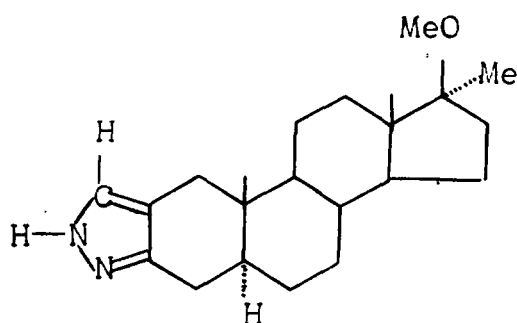
Tindal et al.⁴⁵ have prepared 17 β -hydroxy-17 α -methyl-5 α -androstando[3,2-c]-pyrazole-17-methyl ether (LXXIX) which found use as male contraceptive. A normally fertile 25 year old 70 Kg man was treated twice daily with 10 mg of the compound (LXXIX) for 100 days and rendered infertile. The cyclic ethylene ketal of 17 β -hydroxy-17-methyl-5 α -androstan-3-one was methylated by treatment with Me-I-Ag₂O(Me₂CH)₂NH and then hydrolysed to give, 17 β -methoxy-17 α -methyl-5 α -androstan-3-one (LXXVII). Condensation of (LXXVII) with ethylformate gave the C₂ hydroxymethylene derivative (LXXVIII), which was cyclized with hydrazine to give (LXXIX).



(LXXVII)

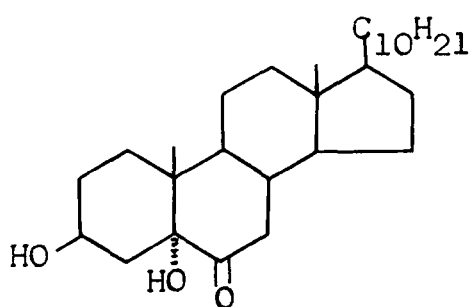


(LXXVIII)

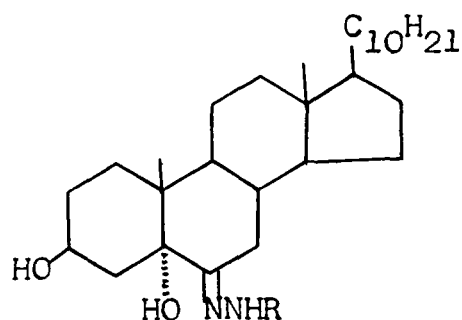


(LXXIX)

Habib et al.⁴⁶ synthesized several steroidal hydrazones in the stigmastane series. They reported 6-arylhydrazono-, aroylhydrazono and thiosemicarbazono-5 α -stigmastane-3 β ,5 α -diol to possess potential antilipenic activity. The stigmastano hydrazones (LXXXIa-d) were prepared from the condensation of 3 β ,5 α -dihydroxystigmastan-6-one (LXXX) with substituted hydrazine. However, the cyclization of these hydrazones leading to the formation of corresponding pyrazoles has not yet been reported.



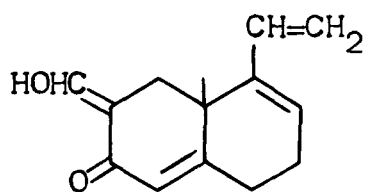
(LXXX)



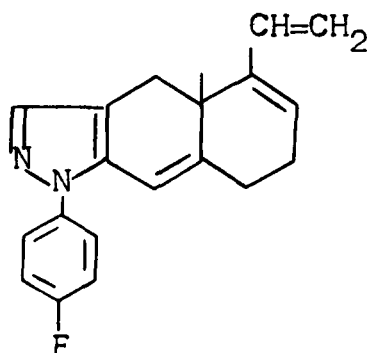
(LXXXI)

- a. R, MeC₆H₄
- b. R, ClC₆H₄
- c. R, HO₂CC₆H₄
- d. R, Bz

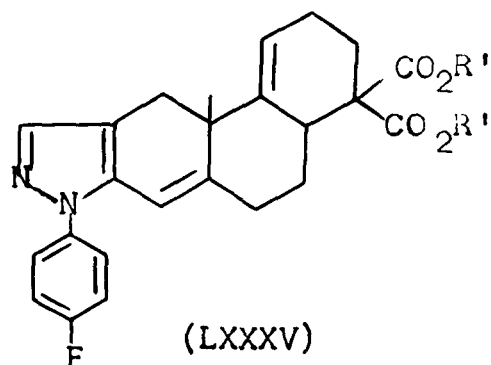
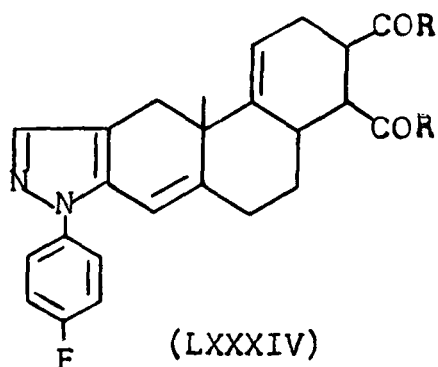
Bell⁴⁷ reported the synthesis of 8H-phenanthro[3,2-c]-pyrazole and found them as antiinflammatory compounds. The condensation of (hydroxymethylene)naphthalenone (LXXXII), with p-fluorophenylhydrazine gave naphthopyrazole (LXXXIII) which was cyclized with 2,5-diketohex-3-ene to give LXXXIV (R = Me). LXXXV (R' = Me) was obtained when condensation was carried out with CH₂=C(COOMe)₂.



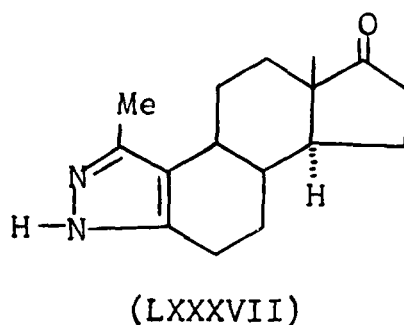
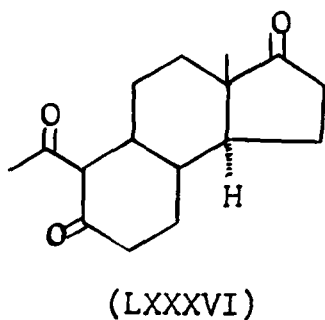
(LXXXII)



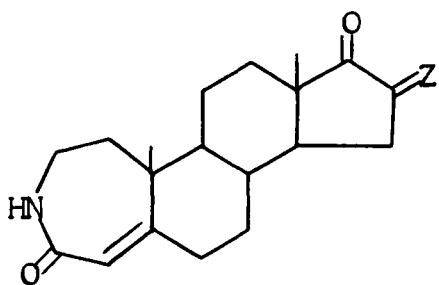
(LXXXIII)



Crabbe et al.⁴⁸ extended the approach to the preparation of novel heterocyclic steroids. The reaction of trione (LXXXVI) with 95% hydrazine hydrate in refluxing alcohol afforded selectively the 1-methyl-2,3-diazo steroid derivative (LXXXVII) in 90% yield. The compound (LXXXVII) in rats shows a high affinity for androgen binding protein (ABP) and it is known that ligands that bind with high affinity to ABP but do not interact with the androgen receptor are potentially inhibitor of male fertility⁴⁸.

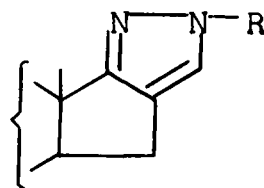


Xenos et al. in 1985⁴⁹ fused [16,17]-pyrazole ring to A-homo steroidal lactams. Condensation of azahomoandrostanone (LXXXVIII) with ethylformate in benzene at room temperature for 120 hrs gave 45% of 16 α -hydroxymethylene derivative (LXXXIX), which on reaction with hydrazine or substituted hydrazine afforded pyrazoloazahomoandrostanes (XC).



(LXXXVIII) Z, H₂

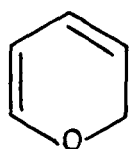
(LXXXIX) Z, CHOH



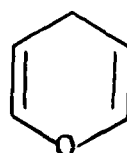
(XC) R, H, Ph, Me

PYRANS

A doubly unsaturated six-membered ring system having an oxygen as heteroatom is known as pyran. The double bonds may be conjugated as in α - or 1,2-pyran (XCI) or isolated as in γ - or 1,4-pyran (XCII). Much attention has been focussed towards the synthesis of compounds having pyran moiety, because of their occurrence in various organic compounds having biological potential^{50a,b}.

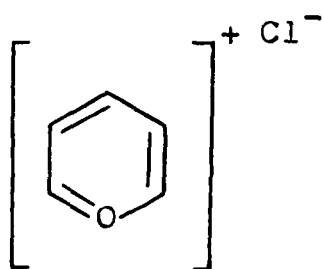


(XCI)

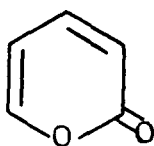


(XCII)

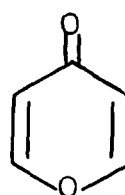
Aromatization of pyran ring involving the removal of a proton and two electrons, leads to the positively charged pyrilium nucleus (XCIII). Whereas replacement of the methylene group of the pyran by a carbonyl group leads to α - or 1,2-(XCIV) and γ - or 1,4-(XCV)-pyrones.



(XCIII)

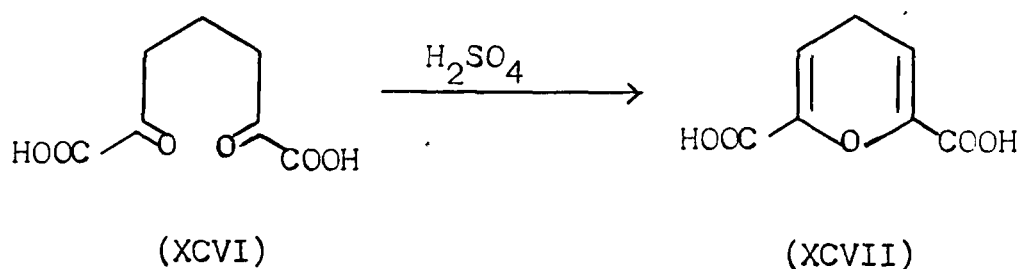


(XCIV)



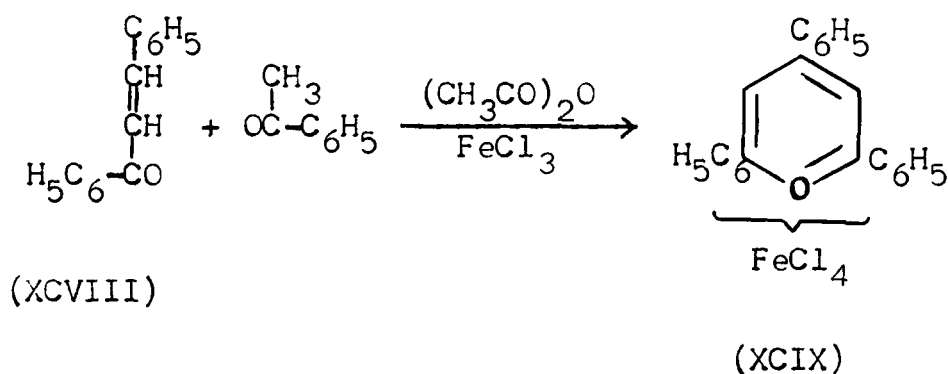
(XCV)

Blaise and Gault⁵¹ have prepared γ -pyran-2,6-dicarboxylic acid (XCVII) by cyclization of α,α' -diketopimelic acid (XCVI) but all attempts to prepare unsubstituted pyran by decarboxylation of (XCVII) have resulted in deep-seated decomposition of (XCVII) itself.

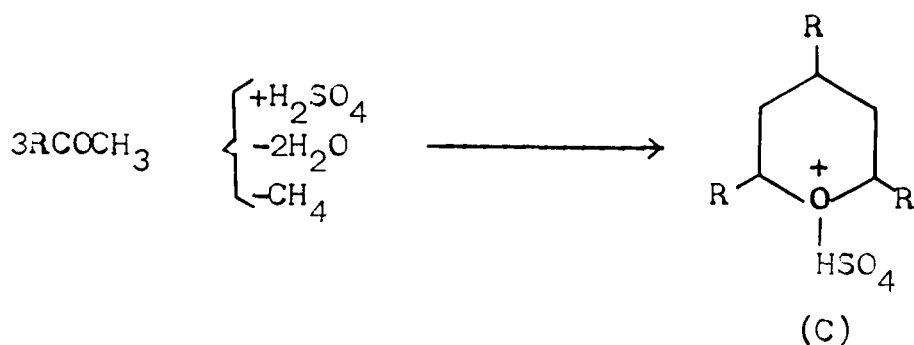


A high degree of stabilization of pyran nucleus is achieved by substituting phenyl groups in 2,4 and 6 positions. Such phenyl substituted pyrans are readily oxidized by mild oxidizing agents to the corresponding pyrilium salts (XCIX) in which the pyran ring has been stabilized by aromatization.

Several methods have been devised for their preparation, of which the one typified by the condensation of benzylideneacetophenone (XCVIII) with acetophenone in the presence of acetic anhydride and ferric chloride has been the most frequently used method^{52a,b} to give pyrilium salt (XCIX).

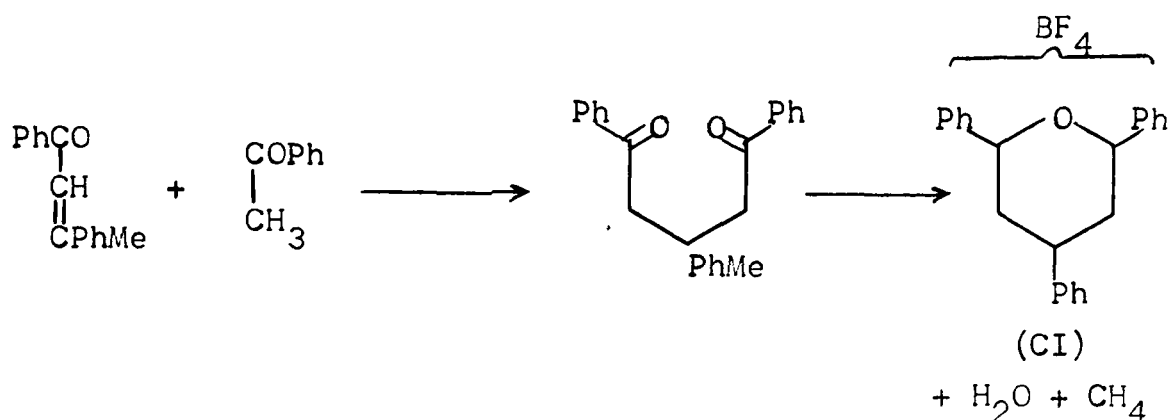


Davis and Armstrong⁵³ reported pyrilium salt during the preparation of sym-trianisylbenzene by the condensation of p-methoxyacetophenone under the influence of a mixture of conc. sulphuric acid and potassium pyrosulphate. They found that 11% of the material is converted to the desired product. Another 11% leads to water soluble bright scarlet crystalline material identified as 2,4,6-trianisylpyrilium acid sulphate (C). This salt was also prepared by Dilthey⁵² in the form of the chloride ferric chloride double salt by reaction of anisal p-methoxyacetophenone with p-methoxyacetophenone in the presence of ferric chloride and acetic anhydride.



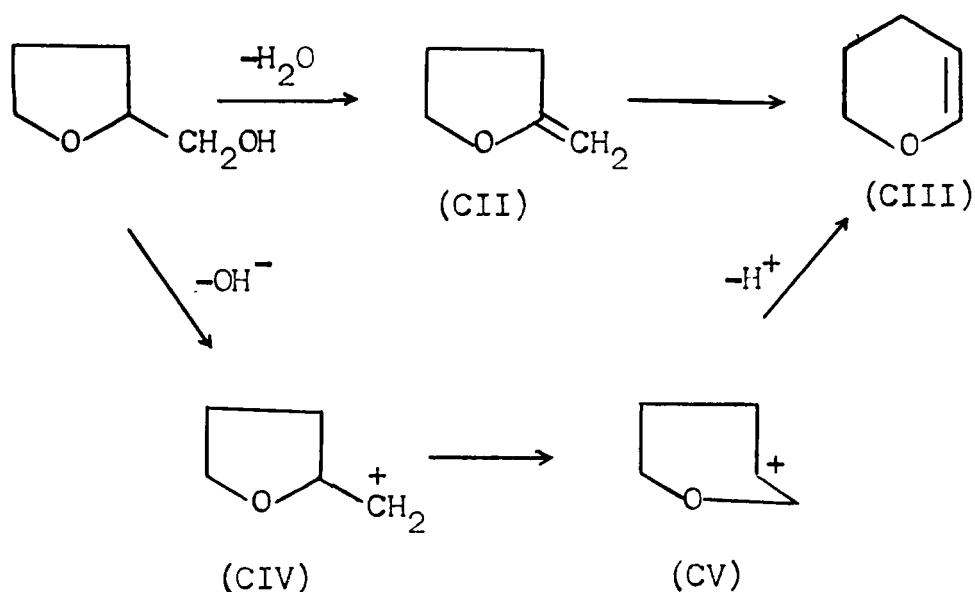
As an extension of the synthesis of β -diketones described by Meerwein and Vossen⁵⁴ by the reaction of methyl ketone and acid anhydride in borontrifluoride, Dovey and Robinson⁵⁵ carried out the same synthesis using acetophenone and obtained 2,4,6-triphenyl pyrilium boronfluoride (CI), convertible into known triphenyl pyrilium ferrichloride (XCIX)⁵². A better yield of the same salt was obtained when an equivalent mixture of acetophenone and phenyl steryl ketone was treated with borotrifluoride.

The mechanism of the reaction (from acetophenone) is obscure. The most probable suggestion is shown below.



In contrast to the alkyl pyrans, dihydropyrans and its derivatives have become a group of easily available and well explored substances, largely through the researches of Paul^{56a-c}. He noted that, when tetrahydrofurfuryl alcohol is passed over activated alumina at temperatures between 300-350°, it is dehydrated and rearranged to dihydropyran (CIII). The reaction is strongly

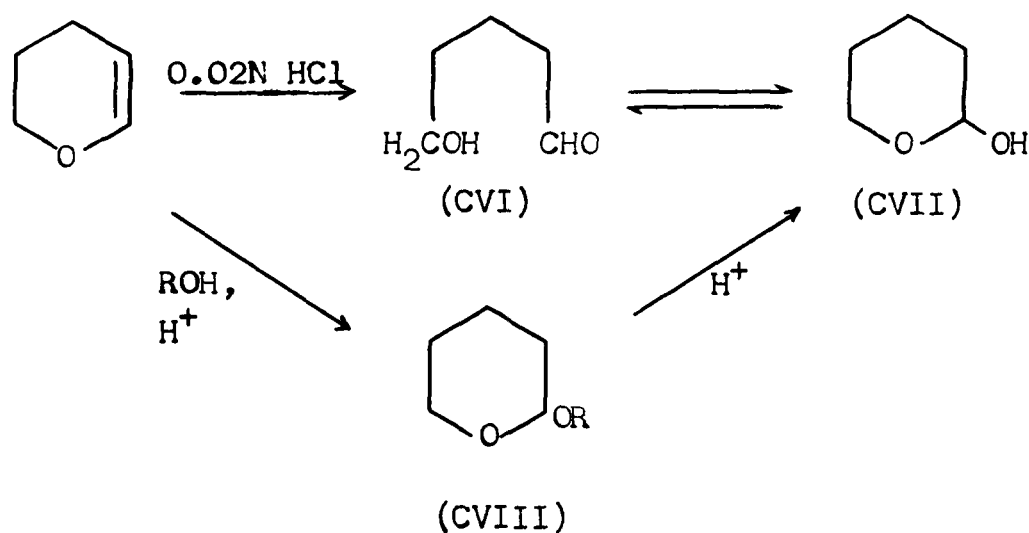
exothermic and may proceed via the unsaturated furan derivative (CII), which has been shown to yield dihydropyran (CIII) under the above conditions or directly by ring enlargement of the carbonium ion (CIV), followed by elimination of a proton from (CV).



A thorough study of the reaction conditions has resulted in substantial improvement in the yields^{57,58} and it is now possible to prepare dihydropyrans in the laboratory in about 85-90% yields.

As a cyclic vinyl ether, dihydropyran is a very reactive substance. It is hydrolysed by acid to 5-hydroxypentanal (CVI)⁵⁷ which exists to the extent of 95% in the tautomeric hemiacetal form (CVII). Under the influence of catalytic amount of hydrogen

chloride, dihydropyran adds alcohol to form inner cyclic acetal (CVIII)^{56,57,59} of the type known as glycopyranosides in carbohydrate chemistry.

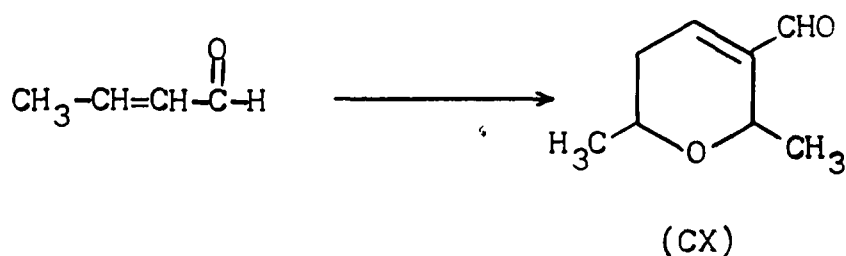


When methyl vinyl ketone is autoclaved in the presence of small amount of hydroquinone in order to prevent chain polymerization, a dimeric substance⁶⁰ is formed in good yield, identified as 2-methyl-6-acetyl- Δ^2 -dihydropyran (CIX).

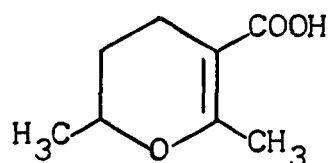


This result, taken in conjunction with the fact that (CIX) does not possess the properties of an α,β -unsaturated ketone, limits the double bond to the 2,3-position. The formation of (CIX) may be pictured as a 1,4-addition of one molecule of the unsaturated ketone to the double bond of the second unsaturated ketone.

A different type of dimerization of α,β -unsaturated aldehydes has been described by Delepine⁶¹, who obtained the dihydropyran derivative (CX) on treatment of crotonaldehyde with dilute acid.

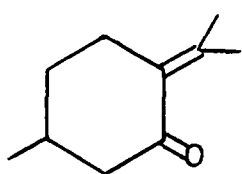


Proof of this structure has been adduced by Delepine and Horeau⁶² in the following manner. On oxidation (CX) yielded an acid, which in the presence of Raney nickel and hydrogen, was not reduced to the expected saturated acid; instead it formed an isomeric acid. The latter was found to be identical with 2,6-dimethyl- Δ^2 -dihydropyran-3-carboxylic acid (CXI), the structure of which had been securely established by Fargher and Perkin⁶³.

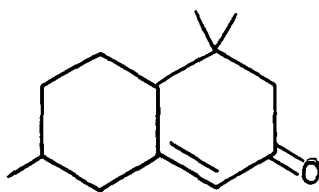


(CXI)

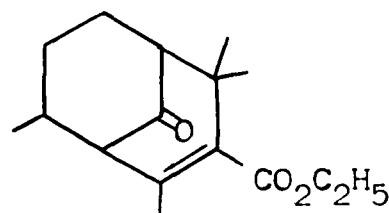
It was shown⁶⁴ that pulegone acetone produced by the zinc chloride catalysed condensation of pulegone (CXII) with ethylacetoacetate, has the constitution represented by (CXIII), rather than three alternate structures proposed by other investigators^{65,66}. In the meantime, Chow⁶⁷ reported the isolation of another crystalline product from the pulegone condensation which was assigned the structure (CXIV).



(CXII)



(CXIII)

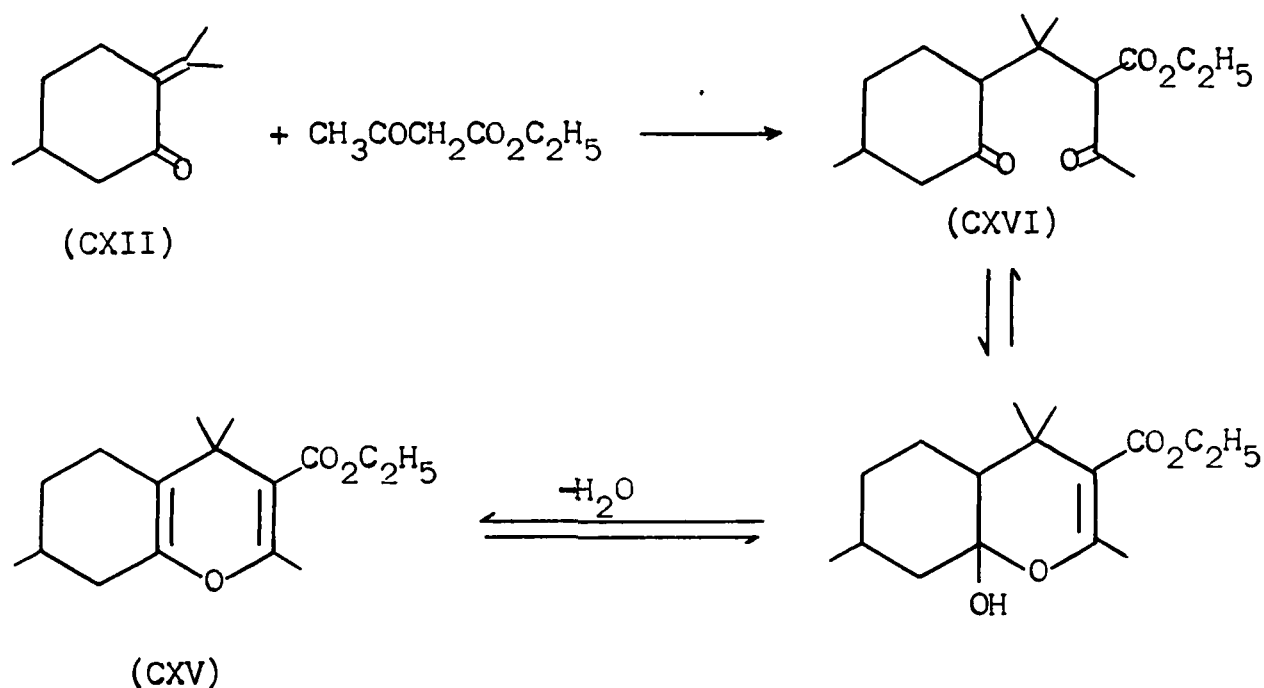


(CXIV)

The exclusive reduction of carboethoxy group in the compound (CXIV) by excess of lithium aluminium hydride and the alleged formation of a hydrazone rather than a normal 2,4-dinitrophenylhydrazone derivative, were two of the many observations reported by Chow⁶⁷, which do not agree with the behaviour expected for a compound

such as (CXIV). Taking the help of all these observations Wolinsky and Hauer⁶⁸ have re-examined the matter and reported that the compound which was expected to be (CXIV) is carboethoxy pyran (CXV) and is most likely to be formed according to the sequence outlined⁶⁸ in scheme-1.

Scheme - 1



When the reaction of pulegone with ethylacetoacetate was conducted for ten hours pulegone acetone (CXIII) was the only crystalline product isolated. When the condensation was stopped after two hours, column chromatography afforded a new crystalline

solid, m.p. 37-38°, whose physical and chemical properties were essentially identical with those of compound (CXIV) reported by Chow⁶⁷.

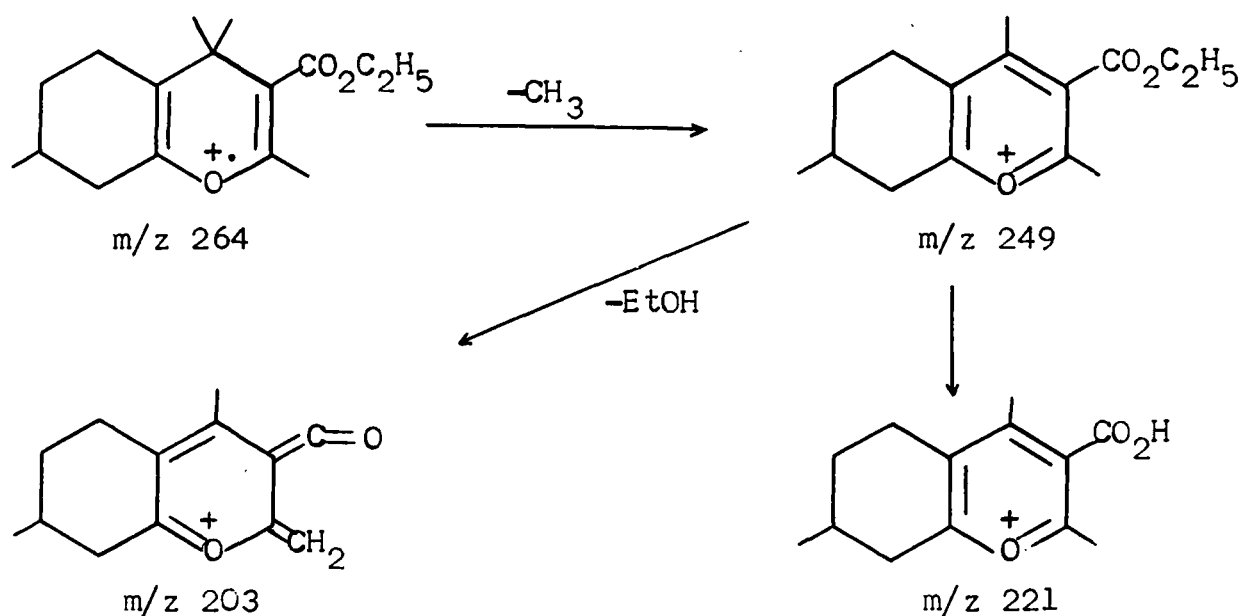
The compound (CXIV) is converted into pulegone acetone (CXIII) by the action of zinc chloride in acetic acid⁶⁷, suggesting that its formation is reversible and the diketoester (CXVI) eventually undergoes an irreversible intramolecular aldol condensation followed by decarboethoxylation to give (CXIII). This accounts for the fact that the compound (CXIV) is not found when the condensation is extended for ten hours. Since the cyclization of (CXVI) to (CXV) produces water, it was reasoned that the yield of (CXV) might be improved if water was removed so as to prevent the hydrolysis of (CXV) to (CXVI). When acetic anhydride is added to reaction mixture, in order to consume the water which was formed, the yield of (CXV) rose from 5 to 18% and little or no pulegone acetone formed. Unfortunately, the yield of (CXV) could not be further improved; the remainder of material was largely accounted for as a nonvolatile, presumed polymeric oil.

The investigation of compound (CXV) began with a spectral examination⁶⁸. The n.m.r. spectrum of compound (CXV) displayed signals at 1.20 and 1.23 ppm accounting for a gem-dimethyl group, a singlet vinyl methyl resonance at 1.90 ppm, a triplet and quartet at 1.28 and 4.11 ppm ($J = 7$ cps) for $-O-CH_2-CH_3$ and most significantly, four protons were accounted for in the region

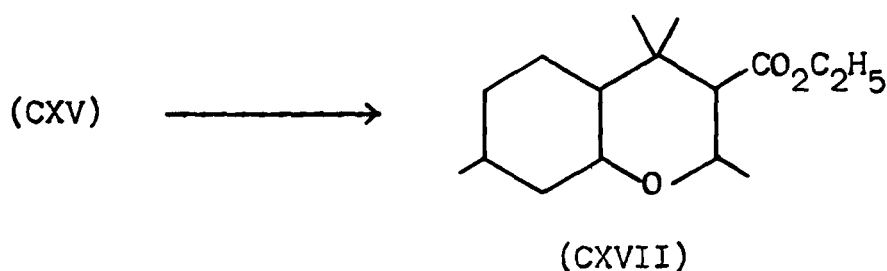
(1.9-2.1 ppm) characteristic of allylic hydrogens. The infrared (1718 and 1633 cm^{-1}) and ultraviolet spectra [λ_{max} 212 and 272 nm (ϵ 2140 and 1480)] were less informative, but are consistent with what might be expected for a carboethoxy pyran^{69,70}. The ultraviolet maxima at 272 nm offers a strong argument against the simple conjugated ester found in Chow's formulation (CXIV).

The mass spectrum of the compound (CXV) showed abundant ions at m/z 249, 221, 219 and 203 in the high mass region. The $M-15$ ion at m/z 249 (37% total abundance) completely dominates the spectrum and provides strong support for (CXV) and its fragmentation to the very stable pyrilium ion as shown in scheme-2.

Scheme - 2



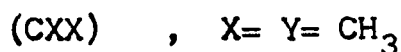
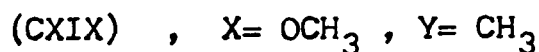
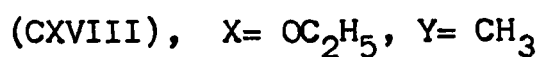
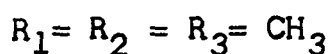
Compound (CXV) displays a plain positive rotatory dispersion curve which confirms the absence of a ketone group. In addition, catalytic hydrogenation gave a tetrahydro derivative (CXVII) rather than a dihydro derivative (CXIV) as reported by Chow⁶⁷ and demonstrates the presence of two carbon-carbon double bonds.



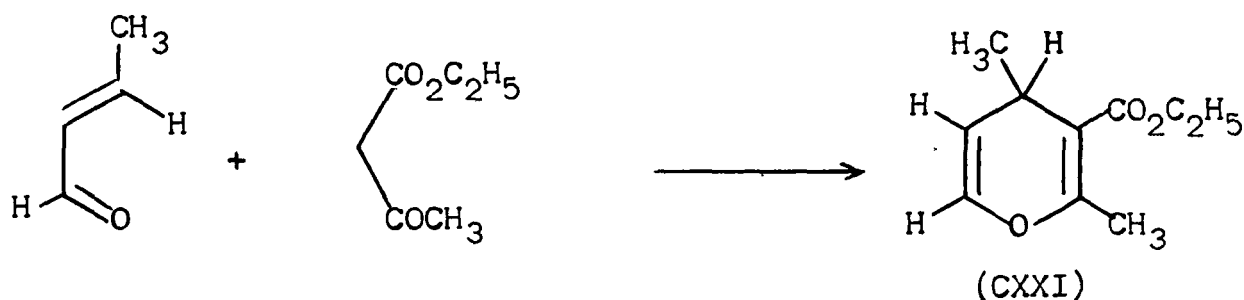
Synthesis of γ -pyran⁷¹ was also achieved by the condensation of β -dicarbonyl compounds with aldehydes or α,β -unsaturated ketones and aldehydes in the presence of zinc chloride. γ -Diketones are readily converted by acid into resonance stabilized furan derivatives while δ -diketones, when subjected to similar conditions, are generally assumed to undergo intramolecular aldol cyclization to cyclohexanone derivatives. γ -Pyran derivatives have only been obtained in cases where structural features, such as lack of an enolizable hydrogen or improper geometric relationships, prohibit the formation of cyclohexanone derivatives. Condensation of α,β -unsaturated aldehydes and ketones with β -dicarbonyl compounds provide a general route to substituted γ -pyran derivatives⁷¹.

Mesityl oxide⁷¹ condenses with ethylacetoacetate, methylacetoacetate, 2,4-pentanedione and ethylbenzoylacetate to give

γ -pyran (CXVIII-CXX), respectively. Although the yields are relatively low (10-25%), the ready availability of starting material and the lack of an alternate route to these compounds makes this an attractive synthetic procedure.

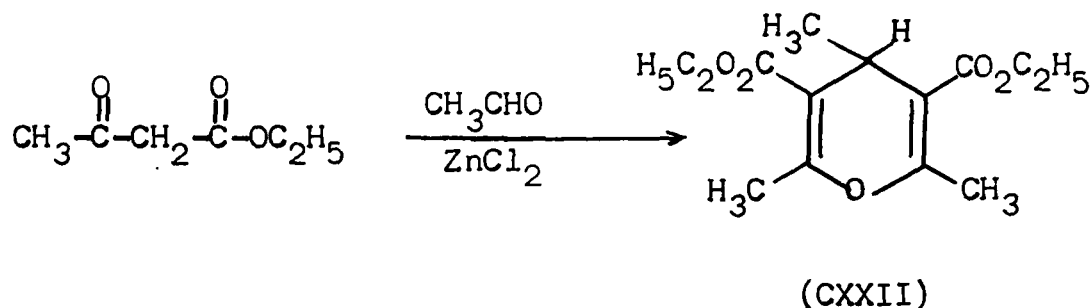


Crotonaldehyde⁷¹ reacts with ethylacetoacetate to give 3-carboethoxy-2,4-dimethyl-4H-pyran (CXXI), which is quite unstable and difficult to obtain in a state of high purity.

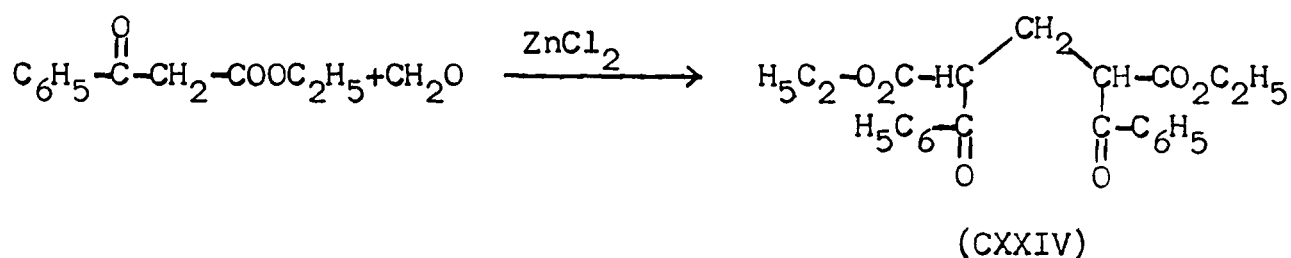
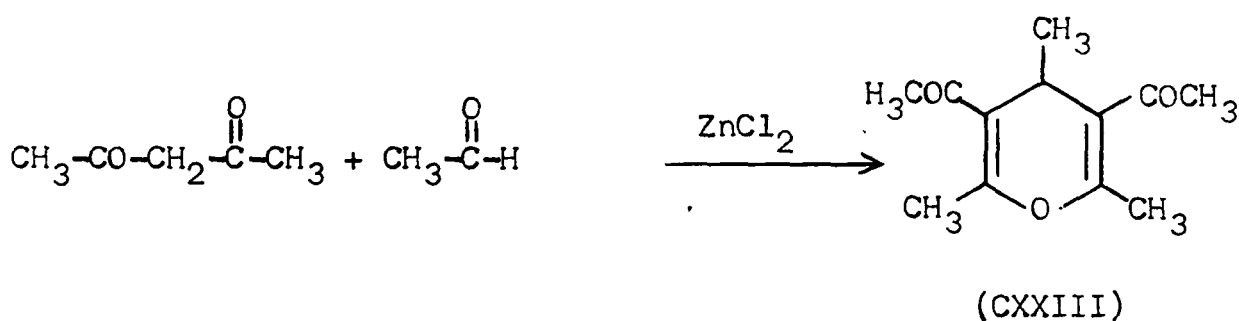


When aldehydes⁷¹ are condensed with ethylacetoacetate in the presence of zinc chloride in acetic acid and acetic anhydride,

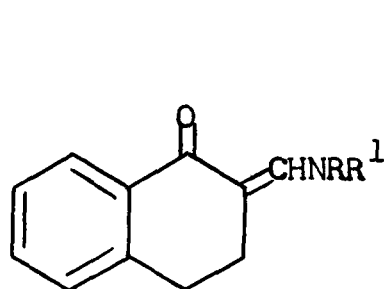
γ -pyran derivatives are produced in 35-50% yields. When acetaldehyde is used the product is (CXXII).



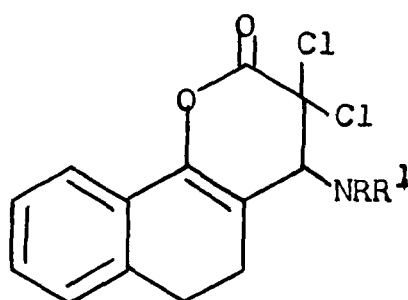
2,4-Pentanedione combined with acetaldehyde in the presence of zinc chloride to give 3,5-diacetyl-2,4,6-trimethyl-4H-pyran (CXXIII)⁷¹. However, ethyl benzoylacetate condensed with formaldehyde to give the δ -diketone (CXXIV), and all attempts to cyclize (CXXIV) to γ -pyran have been unsuccessful.



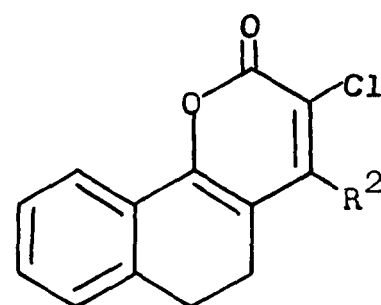
Schenone et al.⁷² in 1974 reported the reactions of (aminomethylene) tetralones (CXXV) ($R = R^1 = \text{CHMe}_2$; $R = \text{Me}$, $R^1 = \text{Ph}$; $R = R^1 = \text{Ph}$) with dichloroketene which undergoes 1,4-addition and forms tetrahydronaphthopyran derivative (CXXVI). Dehydrochlorination of (CXXVI) ($R = \text{Me}$, $R^1 = \text{Ph}$; $R = R^1 = \text{Ph}$) with boiling collidine or Et_3N gave dihydroderivatives (CXXVII).



(CXXV)

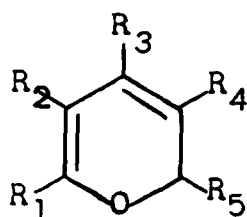


(CXXVI)

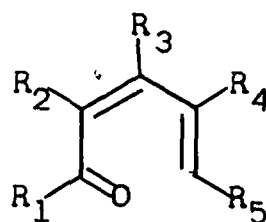


(CXXVII), $R^2 = \text{NRR}^1$
(CXXVIII), $R^2 = \text{H}$

Valence isomerism between 2H-pyran (CXXIX) and cis dienone (CXXX) is a well known phenomenon. The influence of substituents on the equilibrium position has been studied and several synthetic approaches have been applied⁷³⁻⁷⁶. Efforts are concentrated to the preparation of dienones which cyclize to 2H-benzopyrans⁷⁷.



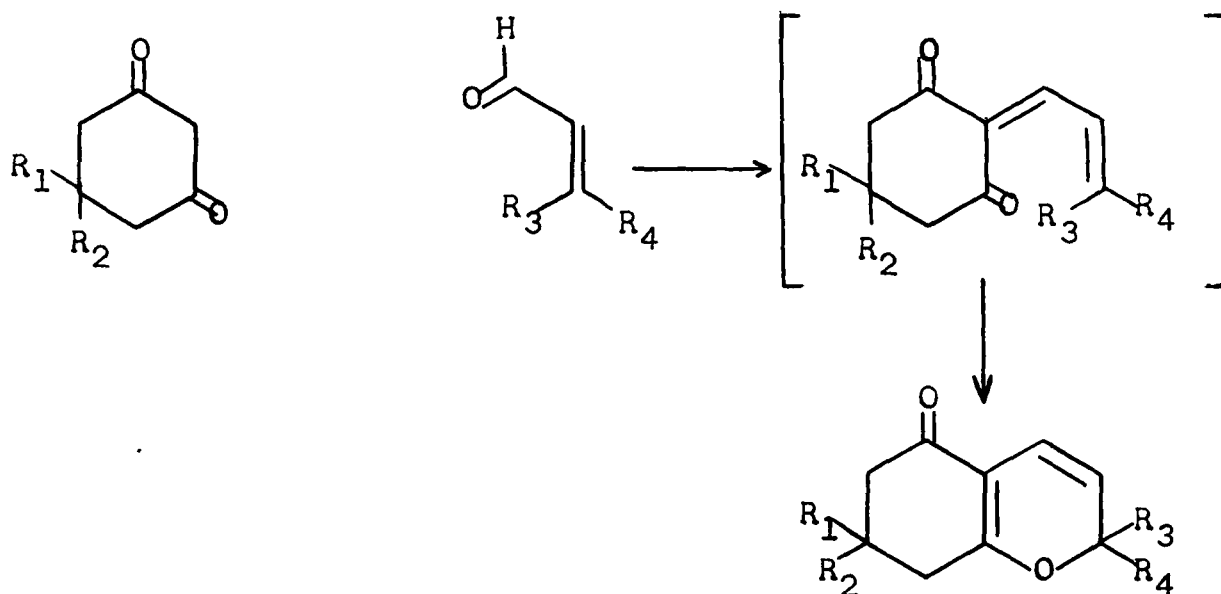
(CXXIX)



(CXXX)

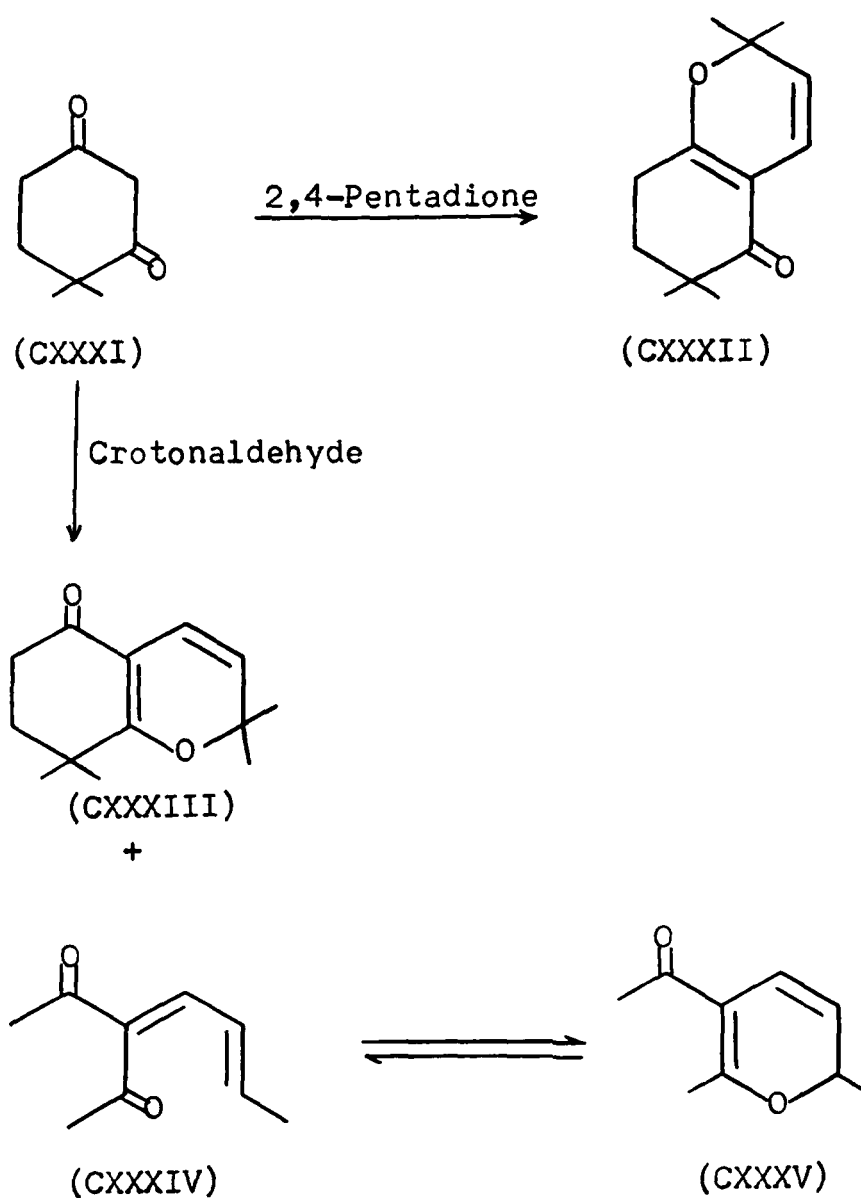
When the 2H-pyran ring is not annelated to an aromatic ring the equilibrium usually favours the cis dienone.

Groot and Jansen⁷⁸ have carried out the simple synthesis of 2H-pyrans. They present a simple and efficient one step synthesis of a non-aromatic annelated 2H-pyran, cis-dienone system, in which the equilibrium is completely shifted to the cyclized product. The intermediate dienones are obtained by condensation of an α,β -unsaturated aldehyde with 1,3-diketone.



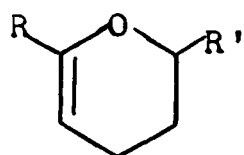
When the reaction is carried out at room temperature a small amount of 1,2-condensation product was isolated⁷⁸ together

with 2H-pyran as the major product. The asymmetric 4,4-dimethyl-1,3-cyclohexanedione (CXXXI) gave the 2H-pyran (CXXXII) and (CXXXIII) and an equilibrium mixture of (CXXXIV) and (CXXXV) with 2,4-pentadione and crotonaldehyde, respectively.



When the 2H-pyran ring becomes annelated to an aromatic ring the intermediate dienones cyclize very rapidly. This has opened useful synthetic routes for several chromones and some alkaloids can also be synthesized very simply and in high yield⁷⁸.

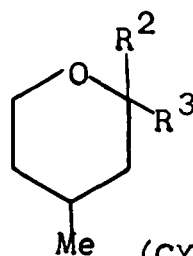
Jenner et al.⁷⁹ in 1977 studied the pericyclic reactions and the effect of pressure in heterodiene synthesis. The condensation of acraldehyde or methyl vinylketone with methyl acrylate, methyl methacrylate, acrylonitrile or 2-cyano-1-propene at 1-300 bar and 130-45° afforded pyran (CXXXVI). Similarly, the condensation of crotonaldehyde with methyl acrylate or methyl methacrylate gave pyran (CXXXVII).



(CXXXVI)

R= H, R'= CHO, CN, CO₂Me

R= Me, R'= Ac, CO₂Me, CN



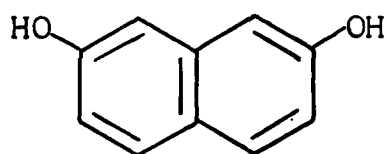
(CXXXVII)

R²= CO₂Me; R³= H, Me

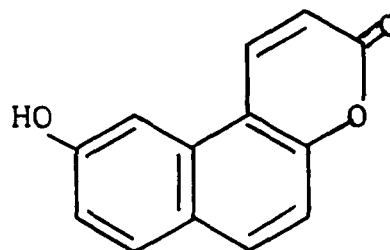
R²= H, Me; R³= CO₂Me

Synthesis of α - and γ -pyrones from various dihydroxy naphthalene have been reported by Pardanani et al.^{80,81}. In 1978 they have reported the synthesis of α - and γ -pyrone derivatives

from 2,7-dihydroxynaphthalene (CXXXVIII). (CXXXVIII) on Pechmann condensation with maleic acid in the presence of conc. sulphuric acid afforded 7-hydroxynaphthd[2,1:6',5']- α -pyrone (CXXXIX).

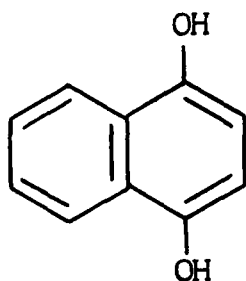


(CXXXVIII)

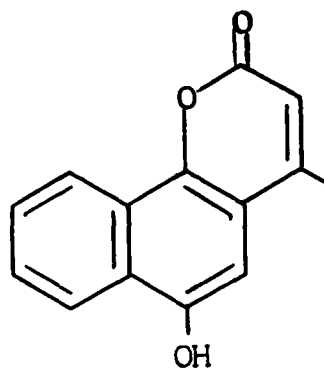


(CXXXIX)

In another communication⁸¹ in 1979 they also reported the synthesis of α - and γ -pyrone derivatives from 1,4-dihydroxynaphthalene (CXL). 1,4-Dihydroxynaphthalene (CXL) on condensation with ethylacetoacetate in the presence of conc. sulphuric acid gave 4-hydroxy-4'-methylnaphtho[1,2:6',5']- α -pyrone (CXLI).



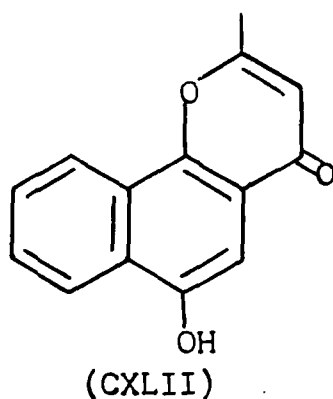
(CXL)



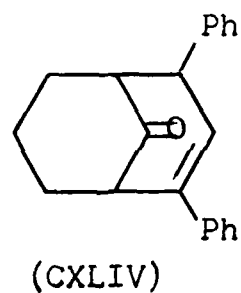
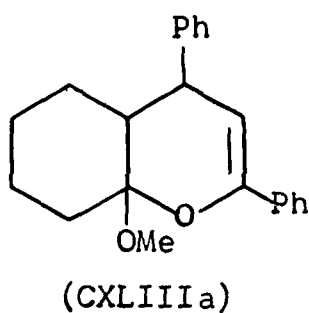
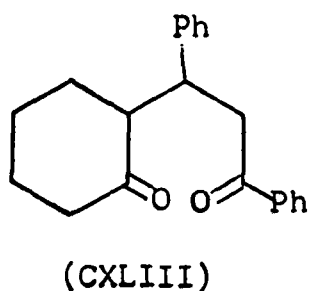
(CXLI)

The γ -pyrone derivative was obtained⁸¹ from 1,4-dihydroxynaphthalene by refluxing it with ethylacetoacetate in

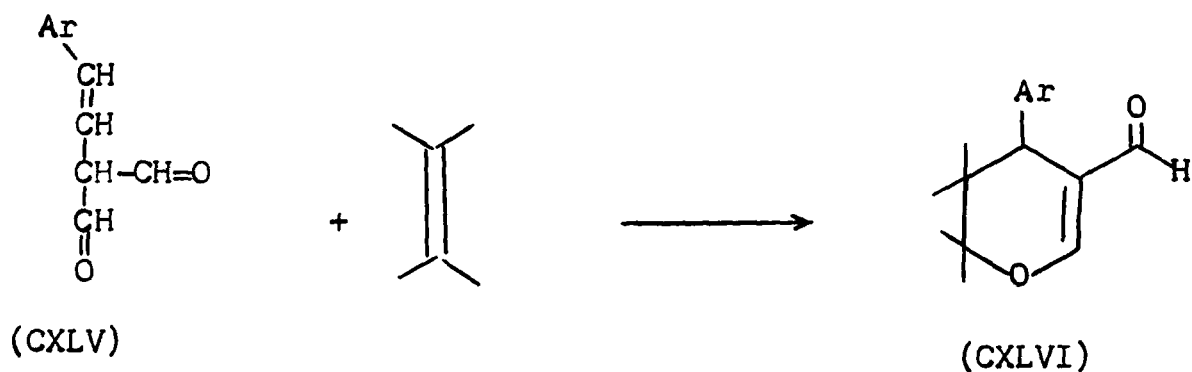
boiling diphenyl ether. It was different from the α -pyrone (CXLI) and on alkaline hydrolysis gave 1,4-dihydroxy-2-acetylnaphthalene. It has been assigned structure as 4-hydroxy-2'-methylnaphtho[1,2:6',5']- γ -pyrone (CXLII)..



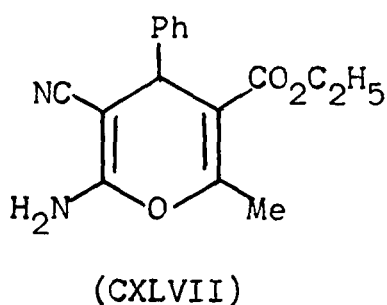
Pyrans have also been reported⁸² from semicyclic 1,5-diketones. Treatment of 1,5-diketone (CXLIII) with methanol and hydrohalic acid gave 60-75% of 1-methoxy-3,5-diaryl-2-oxabicyclo [4,4,0]-dec-3-ene (CXLIIIa) alongwith (CXLIV).



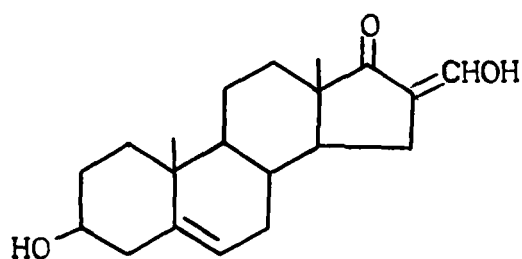
As an example of synthetic potentialities of the studied additions Dvorak and Arnold⁸³ carried out the cyclocondensation of arylmethylenemalonalddehyde (CXLV) with various olefins, as an approach to prepare 4-aryl-3,4-dihydro-2H-pyran-5-carboxaldehyde (CXLVI). It was obtained simply by mixing the two components in an inert solvent in the presence of zinc iodide as catalyst, where yield varies from 58-80%.



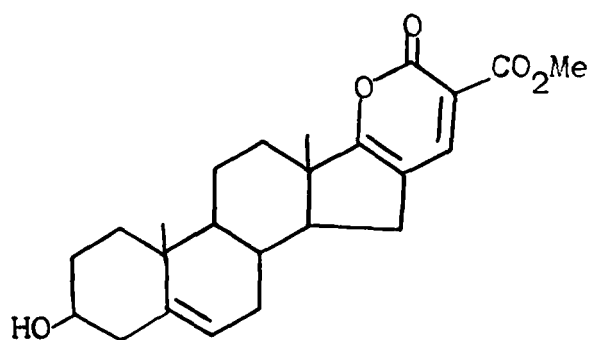
Soto et al.⁸⁴ reported the cycloaddition reaction of dicyanocompounds with α,β -unsaturated ketones. The addition of $\text{PhCH}:\text{C}(\text{CO}_2\text{Et})\text{COMe}$ with dicyanomethane and piperidine gave (CXLVII).



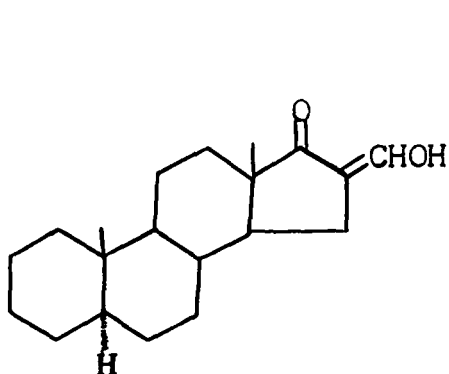
Recently Green et al.⁸⁵ reported the synthesis of 3 β -hydroxyandrost-5-eno[16,17-e]-3'-carbomethoxy-2'-pyrone (CL) and 5 α -androstano[16,17-e]-3'-carbomethoxy-2'-pyrone (CLI). The synthesis has been achieved in one-step from the corresponding hydroxymethylene derivative by using titanium tetrachloride mediated Knoevenagel condensation with dimethyl malonate, which yielded 3 α -hydroxy-16-(hydroxymethylene)-androst-5-en-17-one (CXLVIII) and 16-(hydroxymethylene)-5 α -androstan-17-one (CXLIX).



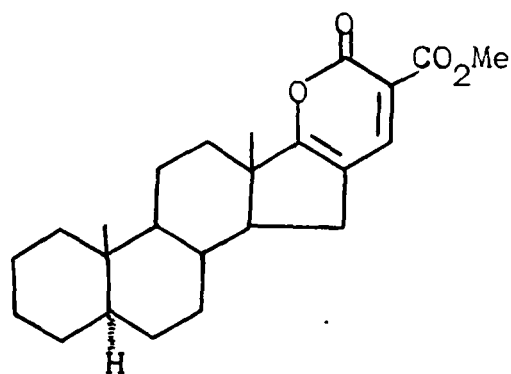
(CXLVIII)



(CL)



(CXLIX)



(CLI)

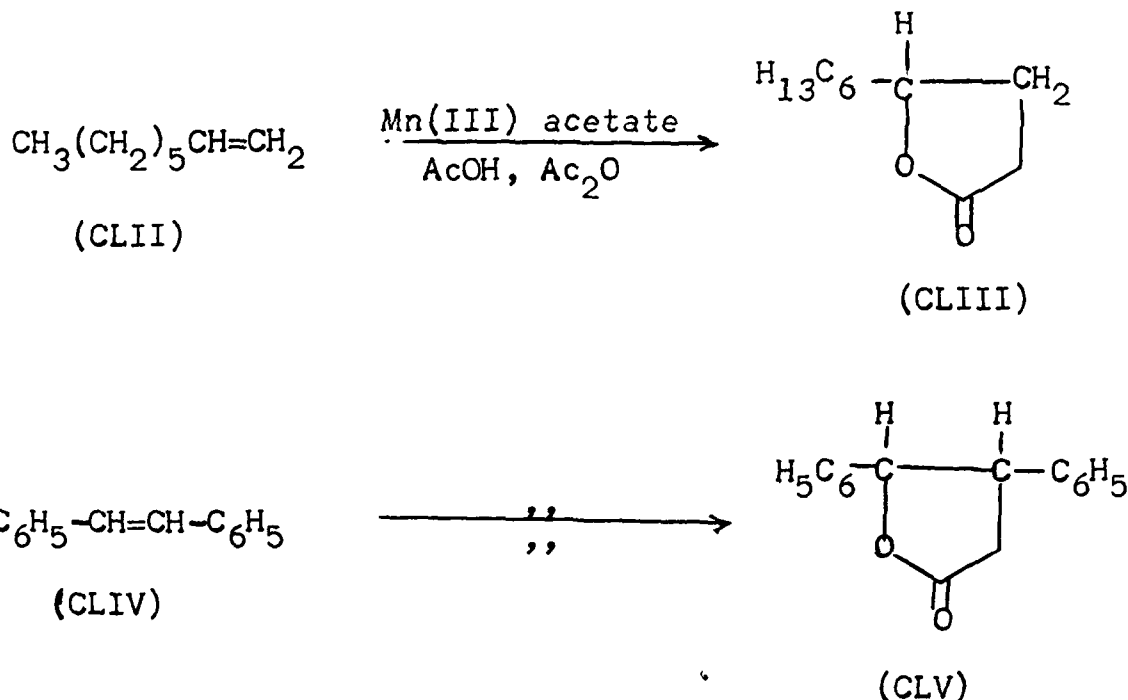
OXIDATION OF OLEFINS WITH Mn(III) ACETATE

Olefins on oxidation with Mn(III) acetate results in the formation of γ -butyrolactones⁸⁶ along with other related compounds, by intramolecular acylation of alcohol function of the intermediate hydroxy acids. The ease with which the lactone ring is formed or broken shows wide variations with change of ring size and with the nature and degree of substitution on ring carbon atom. γ -Lactones are five membered ring compounds which on hydrolysis give γ - or 4-hydroxy acids. Amongst lactones, γ -lactones are regarded as most stable.

Many naturally occurring substances having an unsaturated lactone moiety such as protoanemonin, penicillic acid, clavocin and crepin manifest antibiotic action by the possession of strong antibacterial properties against both gram positive and gram negative bacteria. One of the such simplest substances is protoanemonin first isolated from buttercup by Asahina and Fujita⁸⁷ and later anemone pulsatilla by Baer et al.⁸⁸ Baer and coworkers have investigated the relationship of the structure of simple unsubstituted γ -lactones to antibacterial action. The discovery of pronounced biological properties⁸⁹⁻⁹² has stimulated interests in the simple unsaturated lactones which can be regarded as hydroxy derivatives of furans. Only a few selective examples are being reported in this chapter.

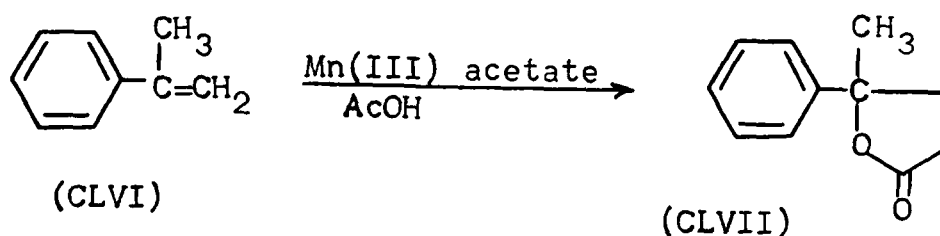
The oxidation of organic compounds by Mn(III) complexes in aqueous solutions has been extensively studied and most of the results have been successfully interpreted in terms of inner sphere one-electron transfer process⁹³.

The oxidation of olefins with leadtetraacetate and other metal complexes has been studied extensively⁹³ but very little is known about of the oxidation of olefins by manganic acetate. Heiba et al.⁹⁴ reported that manganic acetate, a readily accessible reagent⁹⁵ reacts with olefins by a free radical pathway leading to γ -butyrolactones in generally excellent yields. They reported the oxidation of octene-1 (CLII) and trans stilbene (CLIV) with Mn(III) acetate in acetic acid and acetic anhydride which afforded the corresponding γ -lactones (CLIII) and (CLV).



No attempt was made to optimize their yields, which are calculated on the basis of Mn^{3+} consumed. They proposed a mechanism to account for the formation of γ -lactones similar to the one suggested for the lactone component of the leadtetraacetate reactions⁹⁶, except that the necessary carboxymethyl radical is produced directly by thermolysis of the manganic complex. The high yield of the lactone indicated that the carboxymethyl radical adds to the olefin faster than it is oxidized by Mn^{3+} . An expected side product of this reaction is the allylic acetate produced by the abstraction of an allylic hydrogen by carboxymethyl radical.

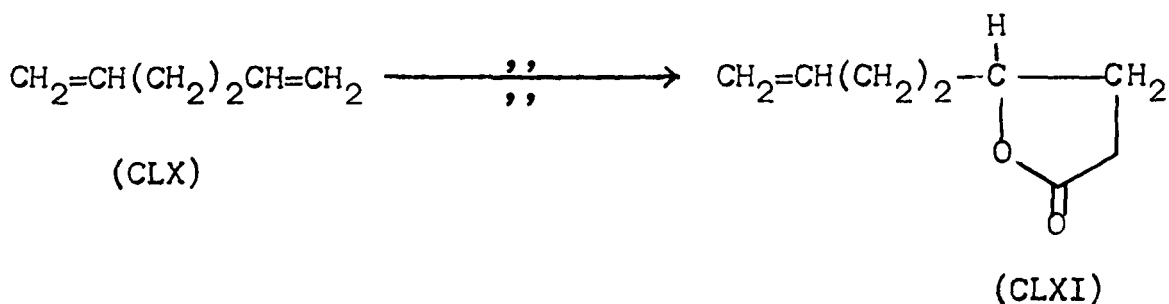
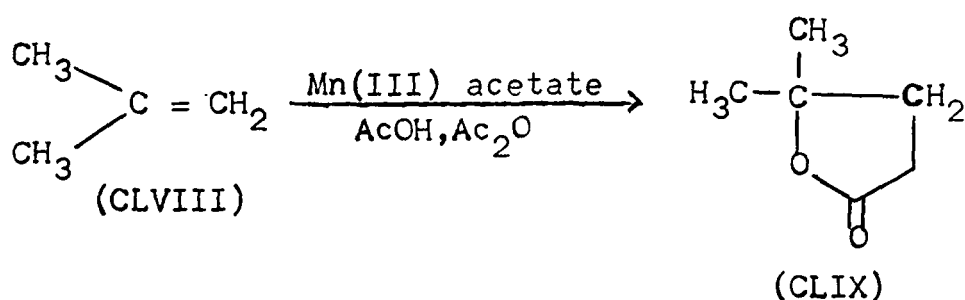
Bush and Finkbeiner⁹⁷ in 1968 have found that solutions produced by dissolving Mn(III) acetate dihydrate in glacial acetic acid reacts with the alkene (CLVI) to give the γ -lactone (CLVII). The formation is explained by interaction of the substrate with an electrophile derived from acetic acid or from acetate group coordinated with the metal.

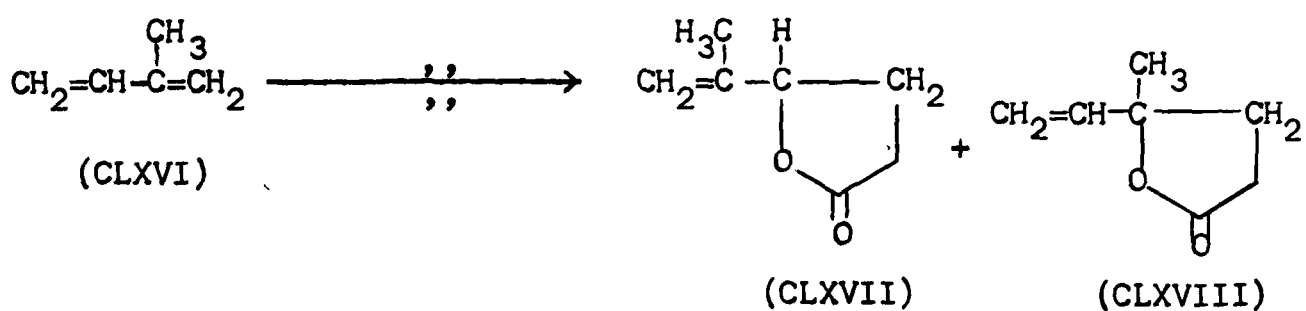
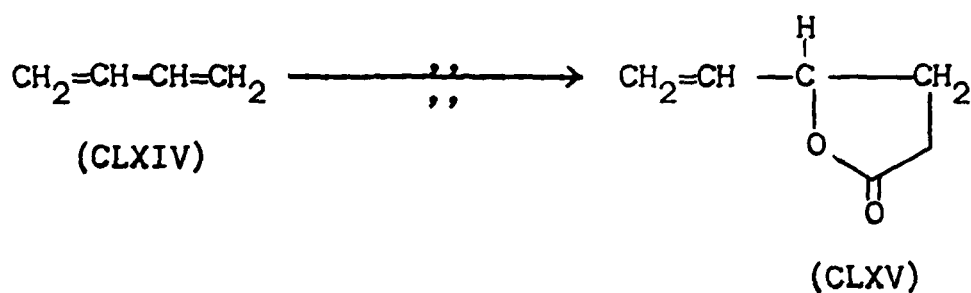
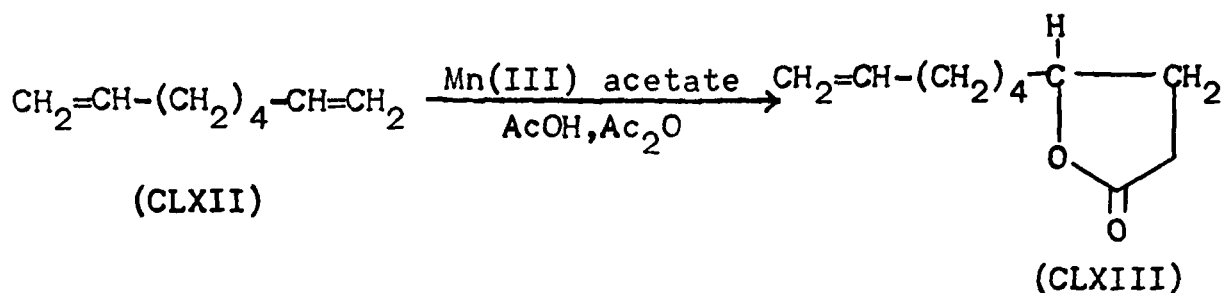


Acetic anhydride has a dramatic effect on the rate of the reaction and yield of the γ -lactone, but not in direct relationship.

Reports have indicated⁹⁷ that rate is enhanced with addition of acetic anhydride but there is downfall in the yield of γ -lactone.

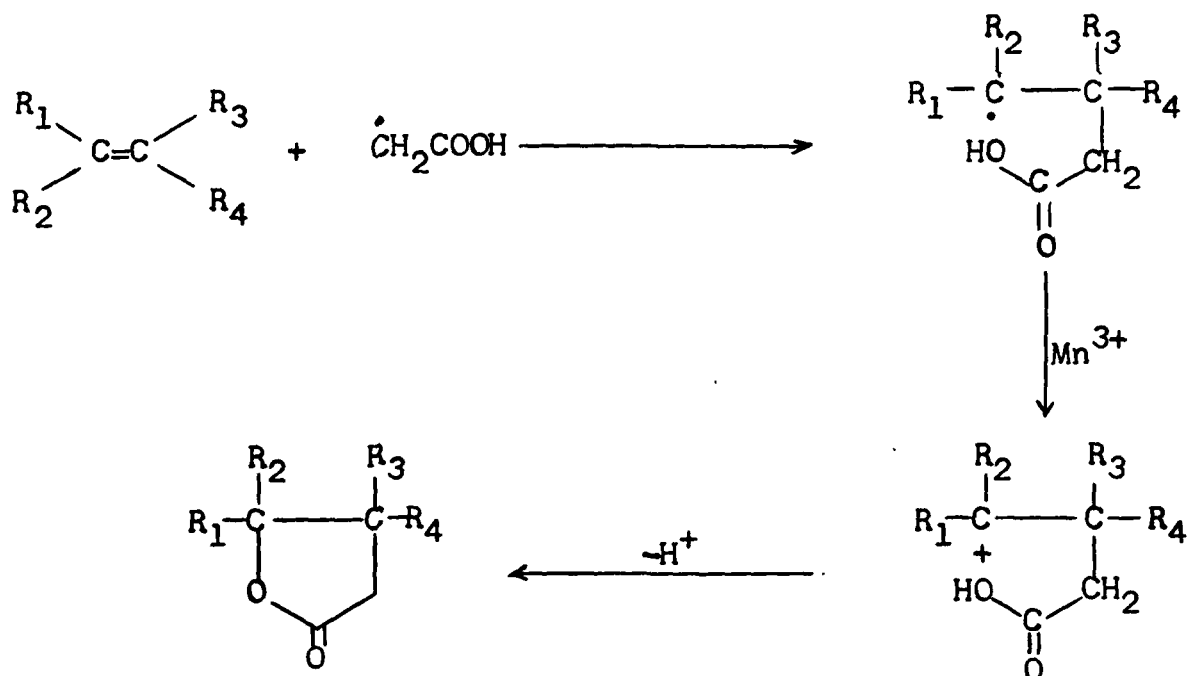
Heiba et al.⁹⁸ reported the synthesis of γ -lactones from olefins with acetic acid. The general reaction consists of the addition of a carboxylic acid, having α -hydrogen atom, across the double bond in the presence of stoichiometric amount of various metal oxidants. For most of the studies manganese compounds are used. They allowed various olefins, such as 2-methyl propene-1 (CLVIII), hexadiene-1,5 (CLX), octadiene-1,7 (CLXII), butadiene (CLXIV), and isoprene (CLXVI) to react with manganese triacetate in presence of acetic acid and acetic anhydride and reported the formation of the corresponding lactones (CLIX), (CLXI), (CLXIII), (CLXV), (CLXVII) and (CLXVIII).



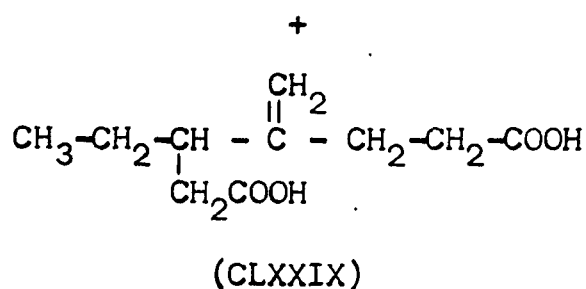
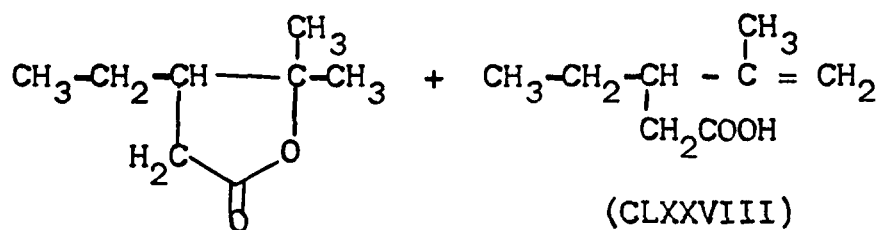
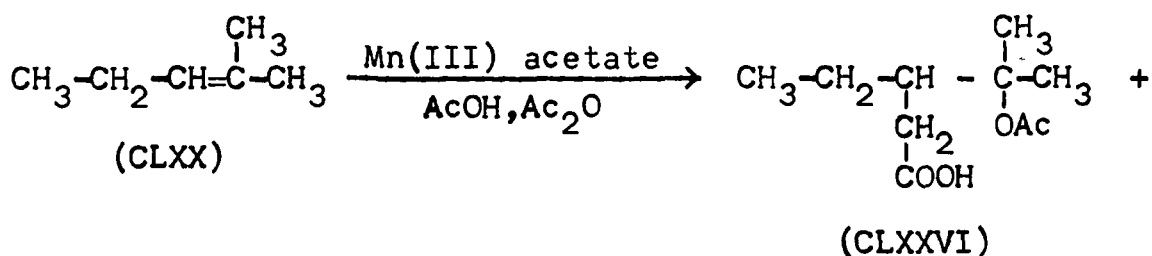
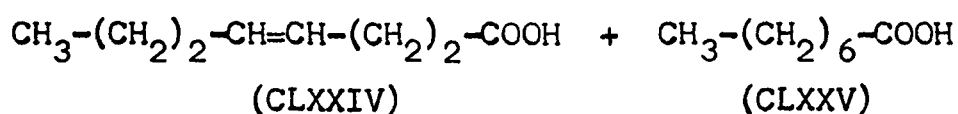
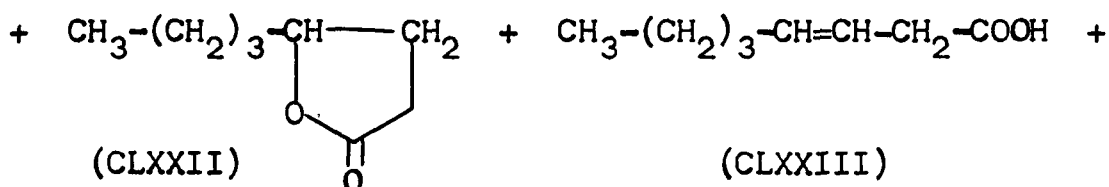
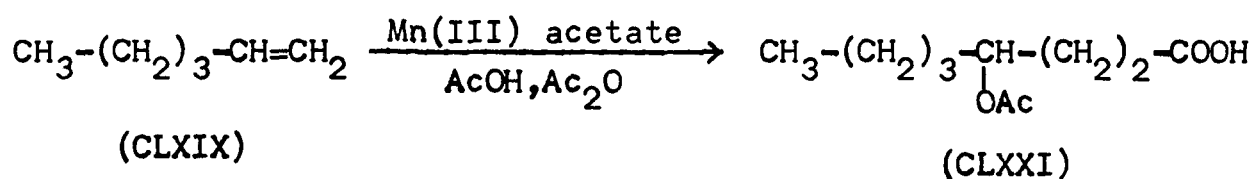


Studies on thermal decomposition of manganic and ceric acetates^{94,99,100} have demonstrated the intermediacy of free carboxy methyl radical. This led to the proposal of the free radical mechanism as shown in the following scheme-3.

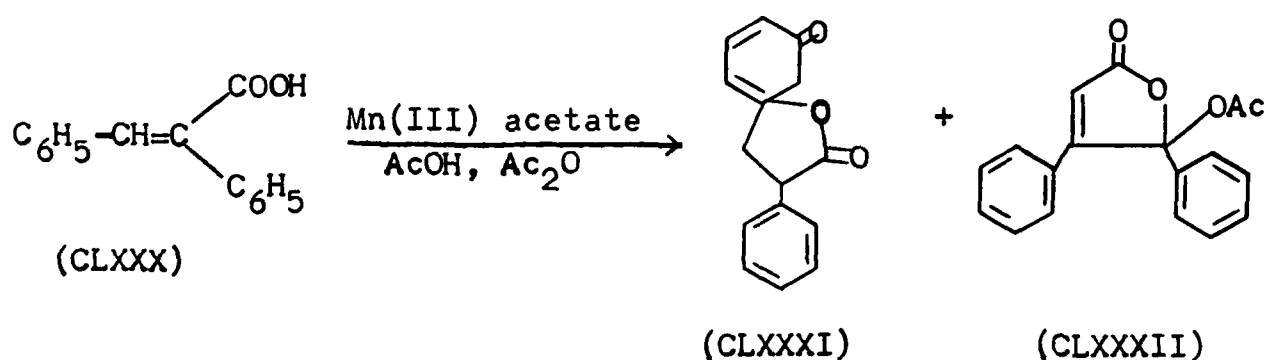
Scheme - 3



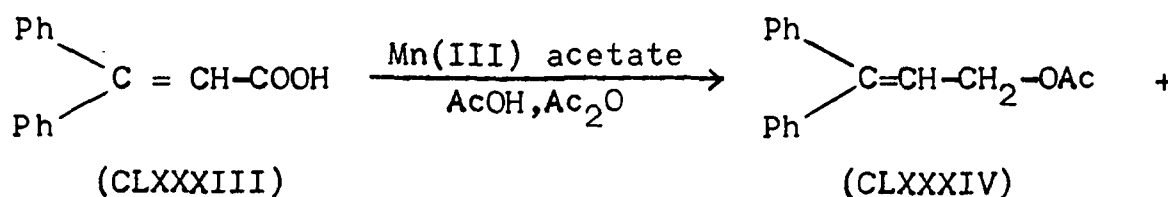
Okano¹⁰¹ reported the oxidation of 1-hexene (CLXIX) and 2-methyl-2-pentene (CLXX) with Mn(III) acetate in presence of acetic and propionic acids. 1-Hexene (CLXIX) afforded 4-acetoxy-octanoic acid (CLXXI), the γ -lactone of 4-hydroxyoctanoic acid (CLXXII), 3-octanoic acid (CLXXIII), 4-octanoic acid (CLXXIV) and octanoic acid (CLXXV) in the presence of acetic acid. 2-Methyl-2-pentene (CLXX) gave 4-acetoxy-3-ethyl-4-methyl pentanoic acid (CLXXVI), γ -lactone of 3-ethyl-4-hydroxy-4-methyl pentanoic acid (CLXXVII), 3-isopropenyl pentanoic acid (CLXXVIII) and 3-ethyl-4-methylene heptanedioic acid (CLXXIX).

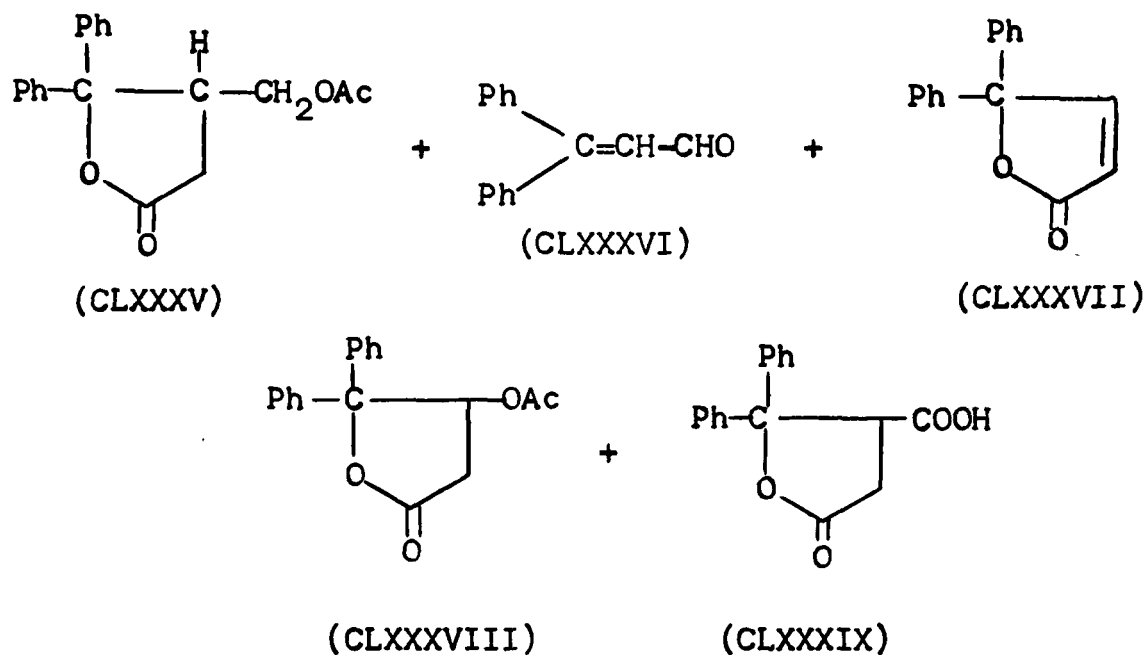


Oishi and Kurosawa¹⁰² in 1980 reported the reaction of α -phenylcinnamic acid (CLXXX) with Mn(III) acetate in the presence of acetic acid and acetic anhydride yielding spirolactone (CLXXXI) and 5-acetoxy-4,5-diphenyl-2(5H)-furanone (CLXXXII).

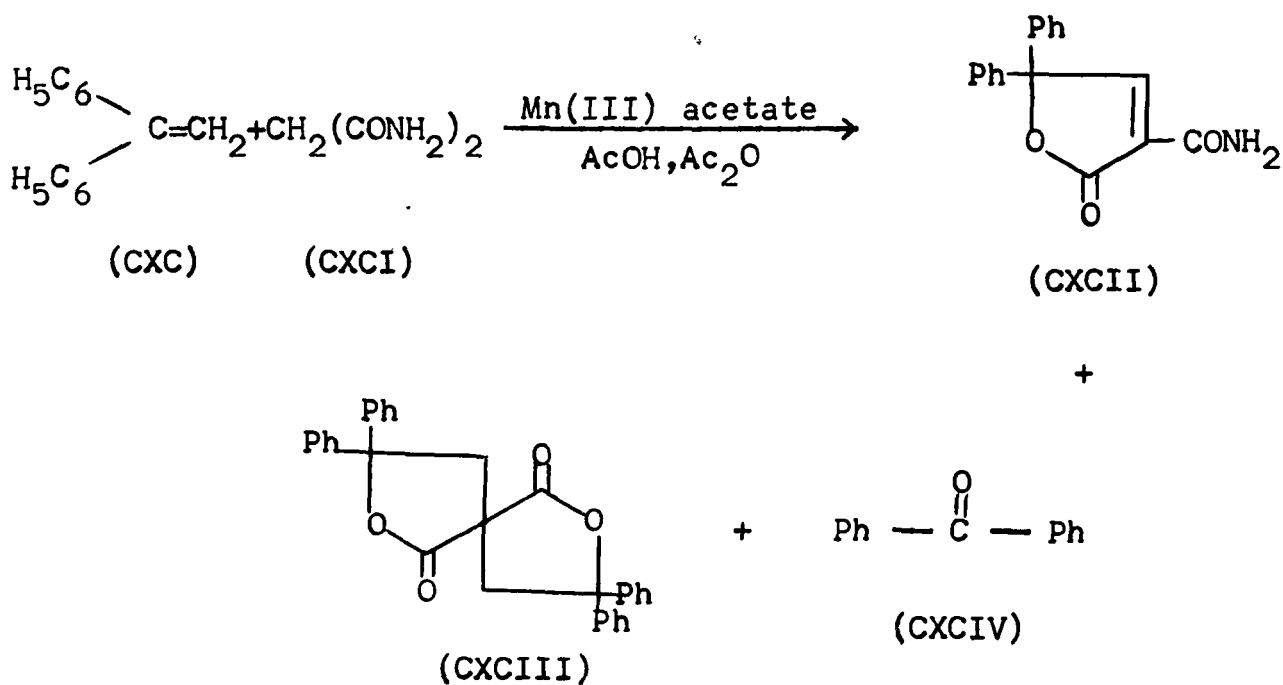


Oxidation of 3,3-diphenyl-2-propenoic acid (CLXXXIII) with Mn(III) acetate in acetic acid gave 3,3-diphenyl-2-propenyl acetate (CLXXXIV), 4-acetoxymethyl-5,5-diphenyl tetrahydro-2-furanone (CLXXXV), 3,3-diphenyl-2-propenal (CLXXXVI), 5,5-diphenyl-2,5-dihydro-2-furanone (CLXXXVII), 4-acetoxy-5,5-diphenyltetrahydro-2-furanone (CLXXXVIII) and 2-oxo-5,5-diphenyltetrahydrofuran-4-carboxylic acid (CLXXXIX)¹⁰³.

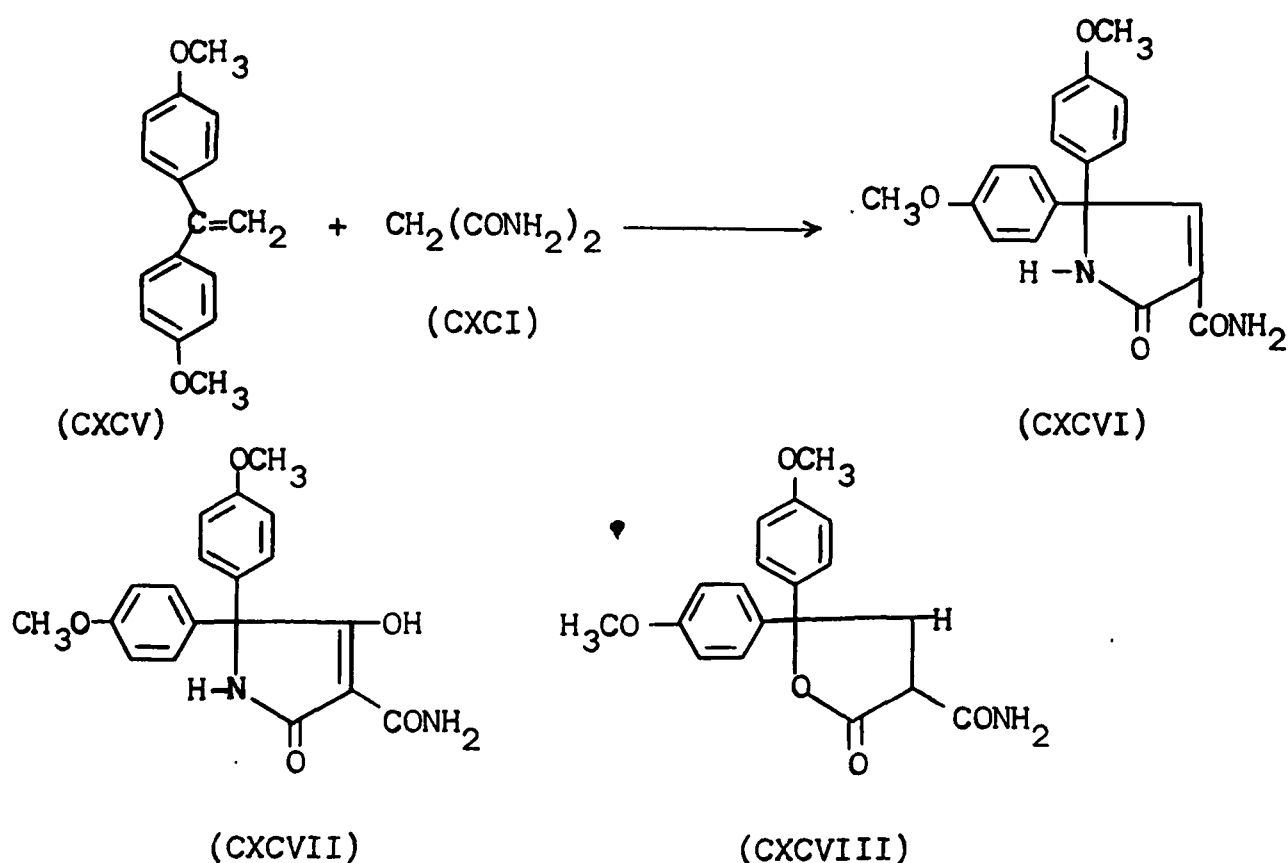




Nishino¹⁰⁴ reported that 1,1-diphenyl ethene (CXC) on oxidation with Mn(III) acetate in the presence of malonamide (CXCI) afforded 2-carbamoyl-4,4-diphenyl-2-buten-4-olide (CXCII), 3,3,8,8-tetraphenyl-2,7-dioxaspiro[4.4]-nonane-1,6-dione (CXCIII) and benzophenone (CXCIV).

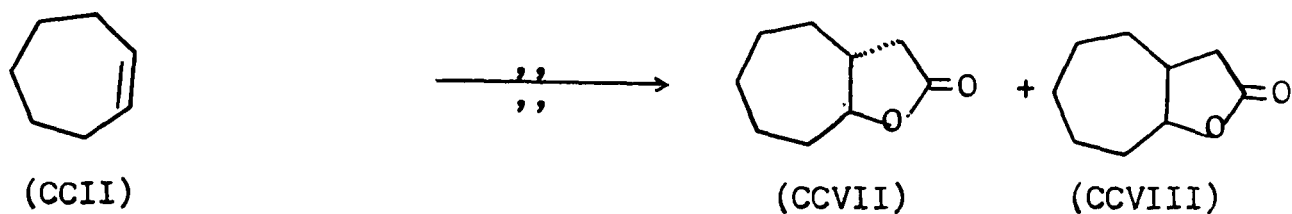
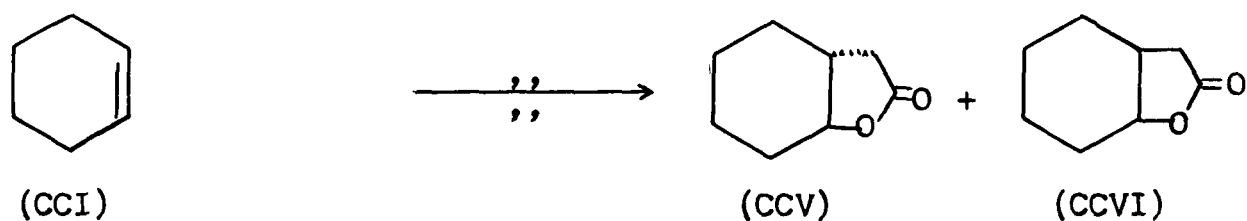
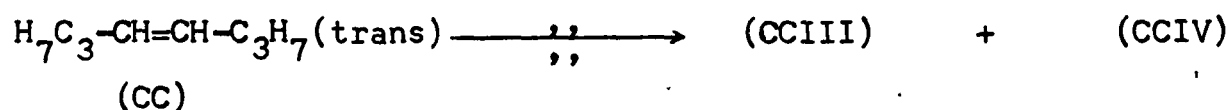
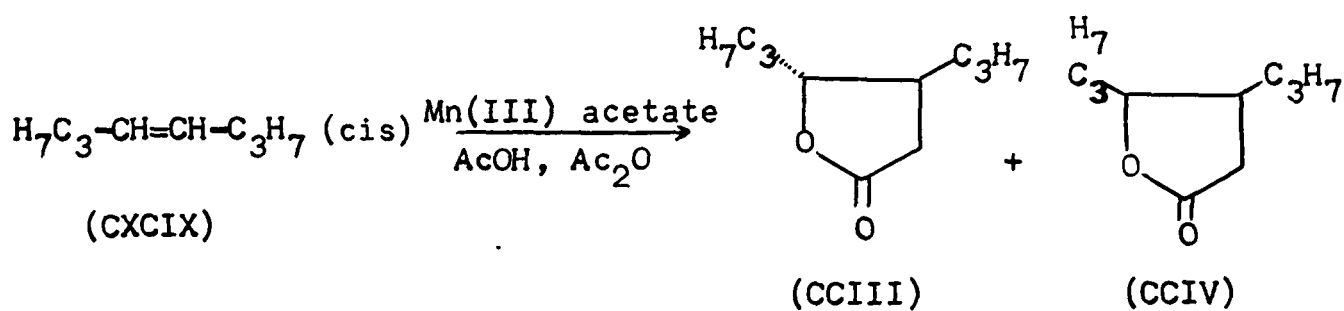


The oxidation of 1,1-bis(4-methoxyphenyl)-ethene (CXCv) under similar conditions afforded α,β -unsaturated- γ -lactams such as 3-carbamoyl-5,5-bis(4-methoxyphenyl)-1H-pyrrol-2(5H)-one (CXCvI) and 3-carbamoyl-4-hydroxy-5,5-bis(4-methoxyphenyl)-1H-pyrrol-2(5H)-one (CXCvII), rather than the corresponding 2-butene-4-olide (CXCvIII)¹⁰⁴.



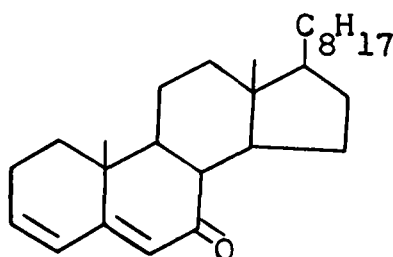
Recently Fristad et al.¹⁰⁵ reported the oxidation of a number of olefins, such as cis octene-4 (CXCIX), trans octene-4 (CC), cyclohexene (CCI) and cycloheptene (CCII) with Mn(III)

acetate in acetic acid and potassium acetate. They afforded their corresponding isomeric γ -lactones, trans-dihydro-4,5-dipropyl-2(3H)-furanone (CCIII), cis-dihydro-4,5-dipropyl-2(3H)-furanone (CCIV), trans-hexahydro-2(3H)-benzofuranone (CCV), cis-hexahydro-2(3H)-benzofuranone (CCVI), trans-octahydro-2H-cyclohepta[b]-furan-2-one (CCVII), cis-octahydro-2H-cyclohepta[b]-furan-2-one (CCVIII).

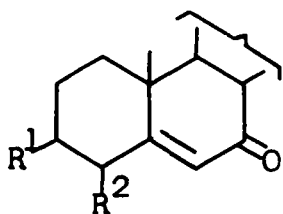


In continuation to their work Fristad et al.¹⁰⁶ in 1985 reported that manganese(III) acetate oxidation of maleic acid in presence of alkene resulted in the formation of spirofused lactones.

Ahmad et al.¹⁰⁷ in 1984 reported the synthesis of γ -lactones in the cholestane series using α,β -unsaturated ketones with Mn(III) acetate. They reported that cholesta-3,5-dien-7-one (CCIX) on reaction with Mn(III) acetate in presence of acetic acid and acetic anhydride afforded 4 β -hydroxy-7-oxocholest-5-en-3 β -yl acetic acid γ -lactone (CCXI). Cholest-5-en-7-one (CCX) afforded lactone (CCXI), alongwith 7-oxocholest-5-en-4 β -yl acetate (CCXb). 3 β -Chlorocholest-5-en-7-one (CCXa) on similar treatment afforded the ketone (CCIX) and the γ -lactone (CCXI).



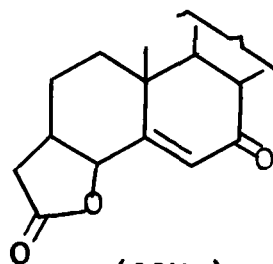
(CCIX)



(CCX) $R_1 = R_2 = H$

(CCXa) $R_1 = Cl, R_2 = H$

(CCXb) $R_1 = H, R_2 = OAc$

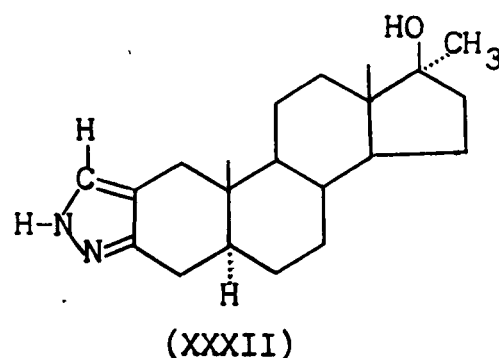
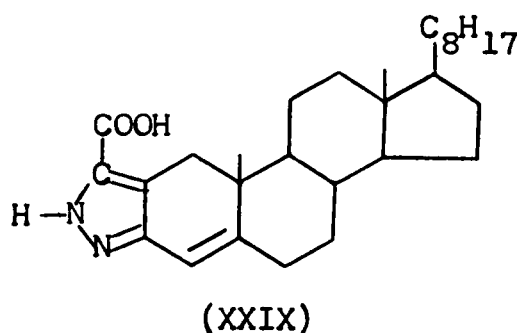


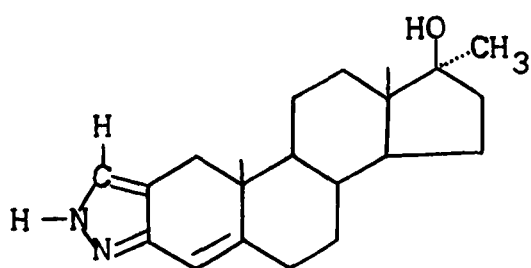
(CCXI)

DISCUSSION

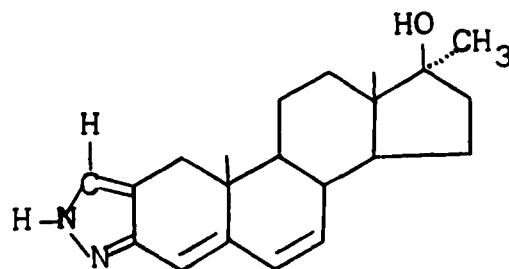
STEROIDAL PYRAZOLES AND PYRAZOLINES

Most of the compounds containing pyrazole nucleus show remarkable and unusual, anabolic and physiological activities³⁴⁻³⁷. This prompted the chemists for their synthesis and investigate such derivatives for their biological activities. The first steroidal pyrazole, cholest-4-eno[3,2-c]-pyrazole-5'-carboxylic acid (XXIX) was synthesized by Ruzicka³³ in 1938. Clinton et al.³⁴ prepared several pyrazoles in androstane series from α,β -unsaturated ketones using phenylhydrazine. They reported the formation of 17 β -hydroxy-17 α -methylandrostano[3,2-c]-pyrazole (XXXII), 17 β -hydroxy-17 α -methylandrost-4-eno[3,2-c]-pyrazole (XXXIV) and 17 β -hydroxy-17 α -methylandrosta-4,6-dieno[3,2-c]-pyrazole (XXXVI). After a considerable span of time much attention has been given by many workers³⁴⁻⁴⁹ towards the synthesis of steroidal pyrazoles and a number of methods have been used. But the most commonly used method is the reaction of hydrazine or substituted hydrazine with α,β -unsaturated ketones.



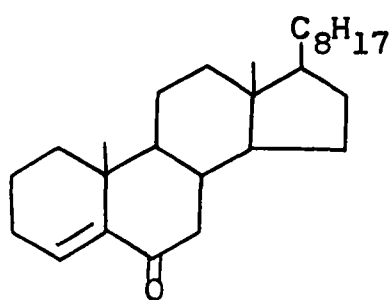


(XXXIV)

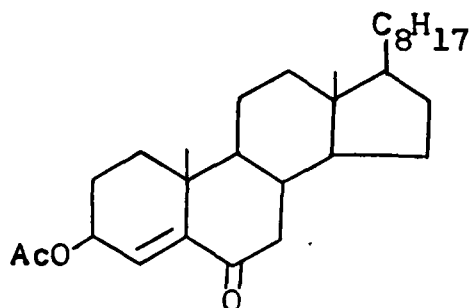


(XXXVI)

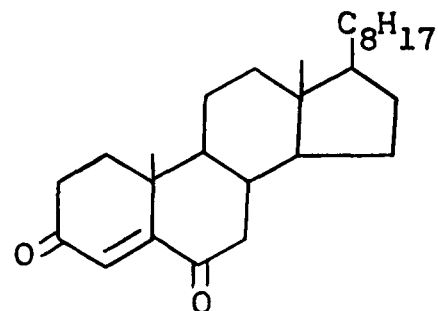
It is worth mentioning here that little attention has been paid towards the synthesis of steroidal pyrazoles in the cholestane and stigmastane series. Prompted by the results obtained earlier, we made attempts to synthesize steroidal pyrazoles from α,β -unsaturated ketones in the cholestane and stigmastane series and phenylhydrazine. For the present study we selected some of the easily accessible α,β -unsaturated ketones such as 4-cholesten-6-one (CCXII), 6-oxo-4-cholesten-3 β -yl acetate (CCXIII), 4-cholestene-3,6-dione (CCXIV), 2,4-cholestadien-6-one (CCXV), 4-cholesten-3-one (CCXVI), 6 β -bromo-4-cholesten-3-one (CCXVII), 4-stigmasten-6-one (CCXVIII), 6-oxo-4-stigmasten-3 β -yl acetate (CCXIX) and 4-stigmastene-3,6-dione (CCXX).



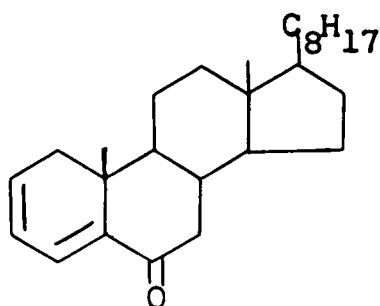
(CCXII)



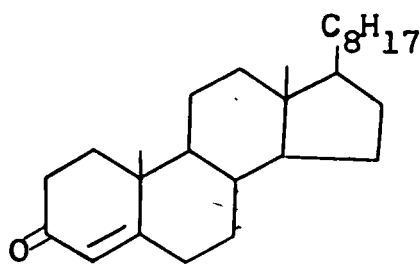
(CCXIII)



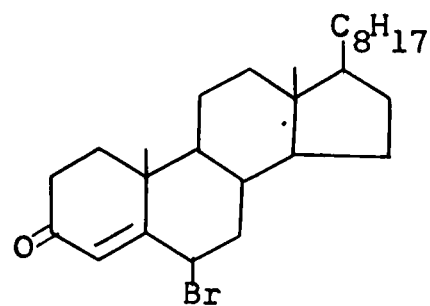
(CCXIV)



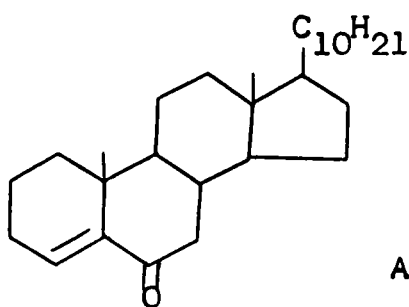
(CCXV)



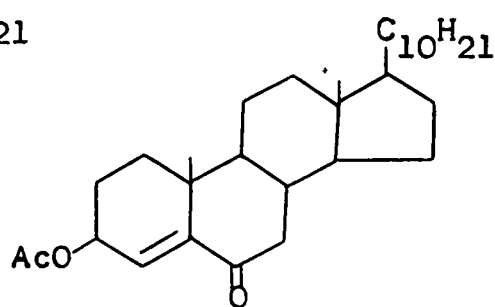
(CCXVI)



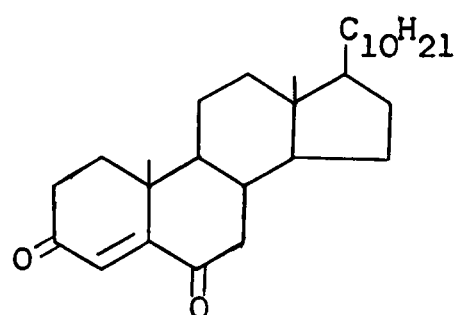
(CCXVII)



(CCXVIII)



(CCXIX)

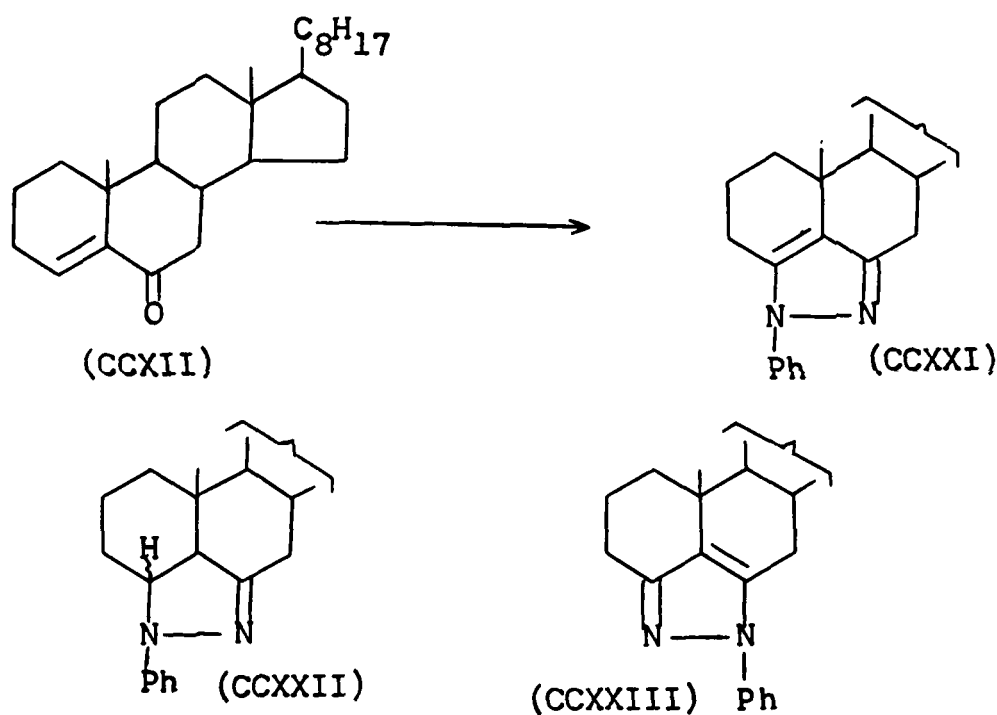


(CCXX)

Reaction of 4-cholesten-6-one (CCXII) with phenylhydrazine
(under atmospheric conditions)

The ketone (CCXII) was prepared according to the literature procedure¹⁰⁸ [ν_{\max} 1685 ($-\text{C}=\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-$), 1625 ($\text{C}=\text{C}$): δ 5.9 br, s (1H, C_4 -vinylic), 2.3 br (2H, C_7-H_2), 1.9 m (2H, C_3-H_2), 1.1, 0.95, 0.8 and 0.7 (methyl protons)]. The spectral data for the ketone were obtained for total identification and for comparison purposes.

The ketone (CCXII)¹⁰⁸ on treatment with phenylhydrazine in acetic acid afforded after usual work up and column chromatography over silica gel a single compound m.p.152^o.

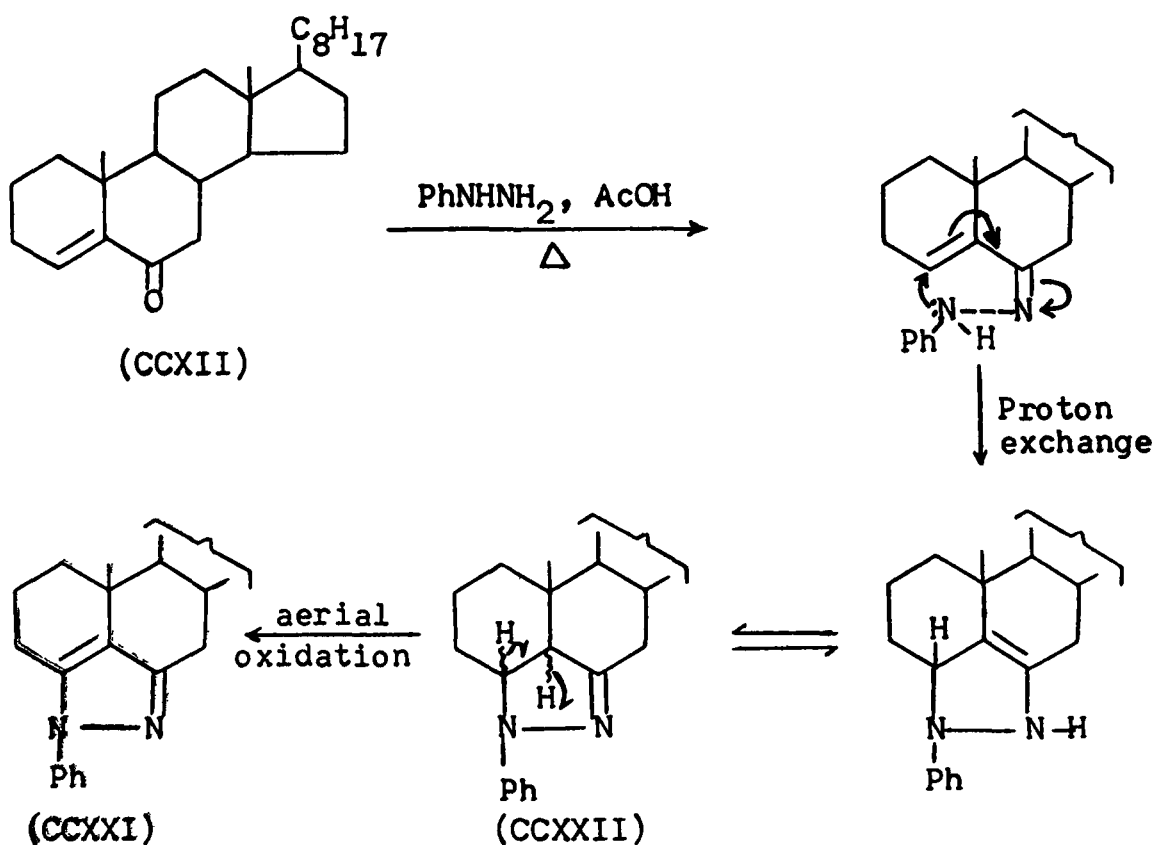


On the basis of earlier reports we may expect three products such as (CCXXI), (CCXXII) and in some cases (CCXXIII)^{10,11} from the above reaction. The compound m.p.152^o gave molecular ion peak at m/z 472 ($\text{C}_{33}\text{H}_{48}\text{N}_2$) and analysed correctly for $\text{C}_{33}\text{H}_{48}\text{N}_2$, which discarded the possibility of structure (CCXXII). The i.r. spectrum showed bands at 3050 w, 1600 m, 1500 s, 750 and 690 cm^{-1} . Bands at 3050 (aromatic C-H), 1600 and 690 (monosubstituted benzene)^{44,109} being characteristic of aromatic rings suggested the

presence of phenyl moiety in the product. The other feature of i.r. spectrum is a band at 1500 cm^{-1} characteristic of C=N vibration¹⁰⁹. At this stage, it was very difficult to distinguish between the structures (CCXXI) and (CCXXIII). Its u.v. spectrum showed absorption maxima at 268 nm which is characteristic of a pyrazole moiety^{44,110}. Its n.m.r. values were observed at δ 7.48 br,m (5H, C₆-H₅), 2.8 br,m (2H, C₇-H₂), 1.9 br,m (2H, C₃-H₂), 1.1 (C₁₀-Me), 0.73 (C₁₃-Me), 0.93 and 0.83 (other methyl protons). The absence of a signal at about δ 4.2 expected for C₄-H as in structure (CCXXII) further discarded its (CCXXII) possibility. On the basis of these values (i.r., n.m.r. and mass) it is not easy and simple to distinguish between (CCXXI) and (CCXXIII). The structure (CCXXI) was however, preferred on the mechanistic grounds. The formation of a pyrazole derivative under these conditions involves dominantly the corresponding phenylhydrazone as an intermediate which cyclizes to give pyrazoline, the latter on aerial oxidation eventually leads to the pyrazole. The exclusive formation of the compound, m.p.152° suggested that the structure (CCXXI) be preferred on the basis of above mentioned mechanistic considerations. However, this is not the only way to get a pyrazole from the interaction of an α,β -unsaturated ketone and phenylhydrazine. Conjugate addition sometime occurs leading eventually to isomeric pyrazole^{10,11}. This indeed seems to be the case when the reaction was conducted under nitrogen where (CCXXI), (CCXXII) and (CCXXIII) were obtained.

The formation of the compound (CCXXI) from the ketone (CCXII) can be shown according to the proposed scheme-4.

Scheme - 4

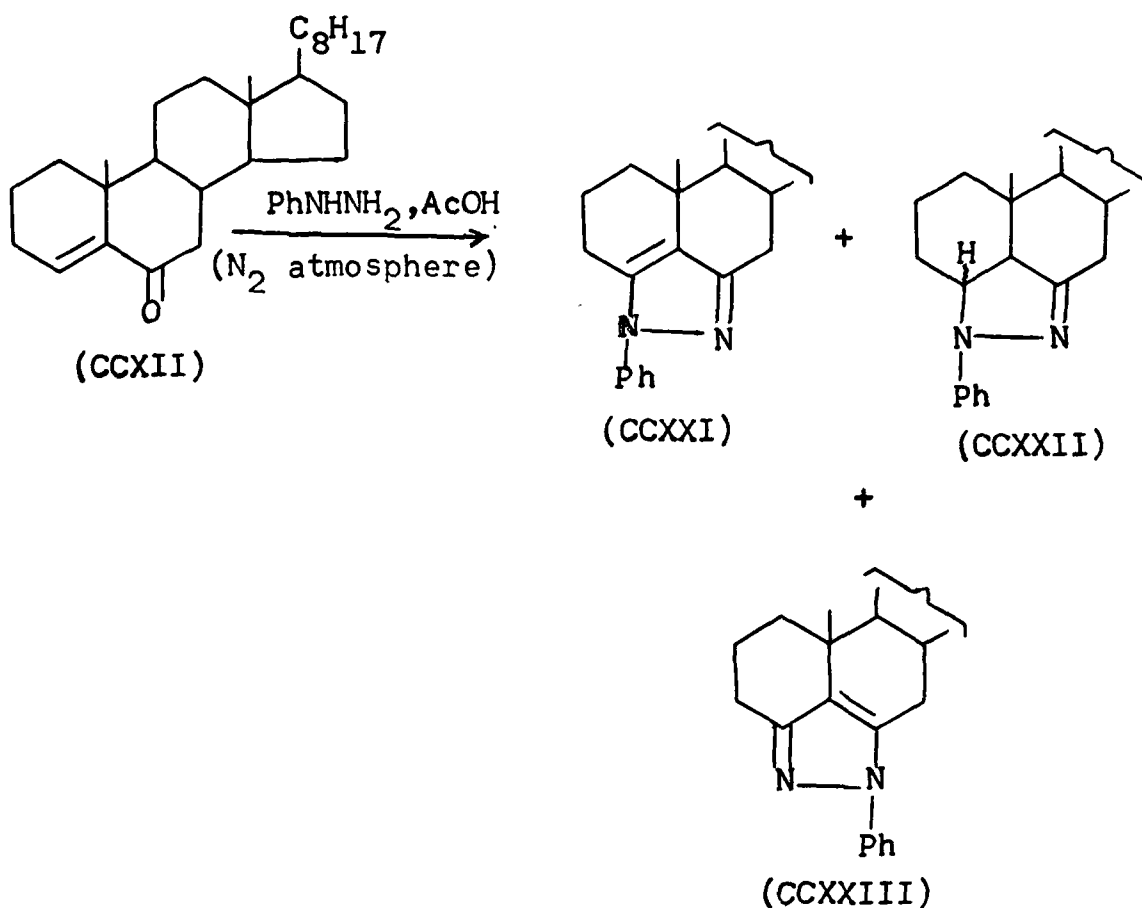


In this mechanism it is proposed that aerial oxidation of pyrazoline (CCXXII) involving free radical mechanism leads to the formation of the compound (CCXXI). It receives further support from the earlier observations¹¹⁰⁻¹¹². However, the intermediate pyrazoline (CCXXII) could not be isolated under the open air reaction conditions.

On the basis of its molecular composition, spectral evidences and general considerations, the compound m.p.152° could be characterized as 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI).

In order to substantiate the intermediacy of the pyrazoline (CCXXII) in the mechanism proposed, the reaction of the ketone (CCXII) was carried out under nitrogen atmosphere.

Reaction of 4-cholesten-6-one (CCXII) with phenylhydrazine
(under nitrogen)



The ketone (CCXXII) on reaction with phenylhydrazine in presence of acetic acid under nitrogen atmosphere after usual work up and column chromatography afforded three compounds oil₁ (CCXXII), (CCXXI, m.p.152°) and another oil₂ (CCXXIII).

Characterization of oil₁ as 2'-phenyl-5 α -cholestan[4,6-cd]-pyrazoline (CCXXII)

The oil₁ analysed for C₃₃H₅₀N₂. Its i.r. spectrum showed bands at 3070 w, 1600 s, 1500, 740 and 690 cm⁻¹. Bands at 3070 w, 1600, 740 s and 690 cm⁻¹ are characteristic of monosubstituted benzene ring and strong band at 1500 cm⁻¹ shows the presence of C=N^{44,109}. Its n.m.r. spectrum displayed a broad multiplet, centred at δ 4.2 with half band width of 13 Hz and integrated for one proton. This signal is best ascribed to C₄-H as in the structure (CCXXII). Apart from the difference in analytical values for CCXXII, CCXXI and CCXXIII which is hardly to be relied upon due to closeness of composition, the signal at δ 4.2 discarded the structures (CCXXI) and (CCXXIII). The other features of n.m.r. spectrum are signals at δ 6.9 br,m (5H, C₆-H₅), 2.7 d (J=12 Hz, 2H, C₇-H₂), 1.1, 0.9, 0.8 and 0.63 (methyl protons). An unresolved doublet but not accounting for one full proton was observed at δ 3.3 which could be assigned to C₅- α H in the structure (CCXXII). These spectral data supported the structure (CCXXII). The pyrazoline (CCXXII) when left

at room temperature started changing into (CCXXI) within a couple of hours and autooxidized completely within 24 hours. The lead tetraacetate oxidation¹¹³ of (CCXXII) into (CCXXI) was found to be complete within 20 minutes.

Thus on the basis of spectral values, chemical transformation and mechanistic consideration the oil₁ can be characterized as 2'-phenyl-5 α -cholestan [4,6-cd]-pyrazoline (CCXXII).

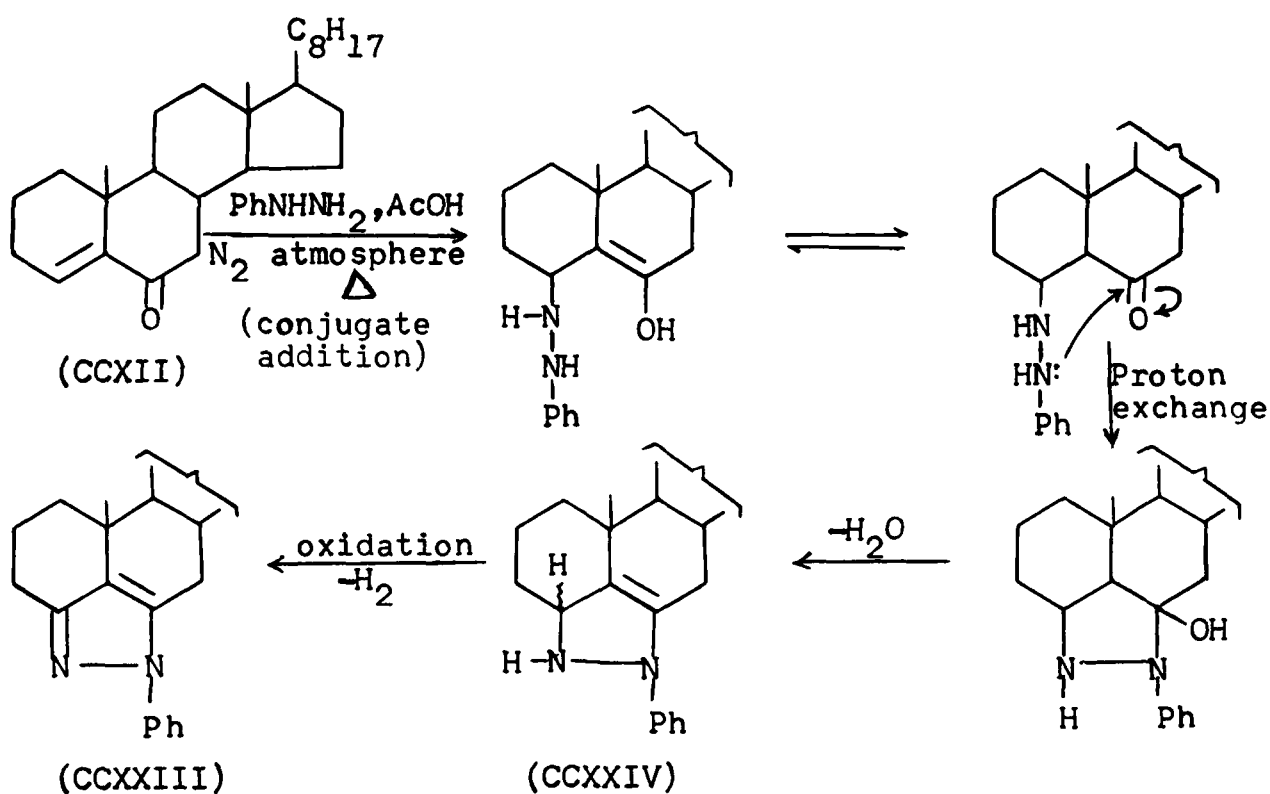
The second product of this reaction having m.p.151-152° was identical in all respects (t.l.c., m.p., m.m.p., i.r. and n.m.r.) with the compound (CCXXI) obtained from the reaction of ketone (CCXII) with phenylhydrazine under atmospheric conditions.

Characterization of oil₂ as 2'-phenyl-5-cholesteno[6,4-cd]-pyrazole (CCXXIII)

The oil₂ analysed for C₃₃H₄₈N₂. Its i.r. spectrum showed bands at 3060 w, 1600 s, 1500 s, 760 and 690 cm⁻¹ (characteristic of phenylpyrazole derivatives). Its u.v. spectrum showed absorption maxima at (λ_{max}) 267 nm which also supported the presence of pyrazole moiety. The n.m.r. spectrum of oil₂ displayed signals at δ 7.5 br,m (5H, C₆-H₅), 2.8 br,m (2H, C₃-H₂), 1.90 br,m (2H, C₇-H₂), 1.10 (C₁₀-Me), 0.70 (C₁₃-Me), 0.90 and 0.80 (other methyls). It is to be noted, near about these values were also recorded for the isomer (CCXXI). However, this compound oil₂ showed difference in

t.l.c. These values, however, are compatible with the structure (CCXXIII). The formation of (CCXXIII) involves conjugate addition of phenylhydrazine on to α,β -unsaturated ketone moiety of (CCXII). Scheme-5 records the probable steps involved in the reaction.

Scheme - 5

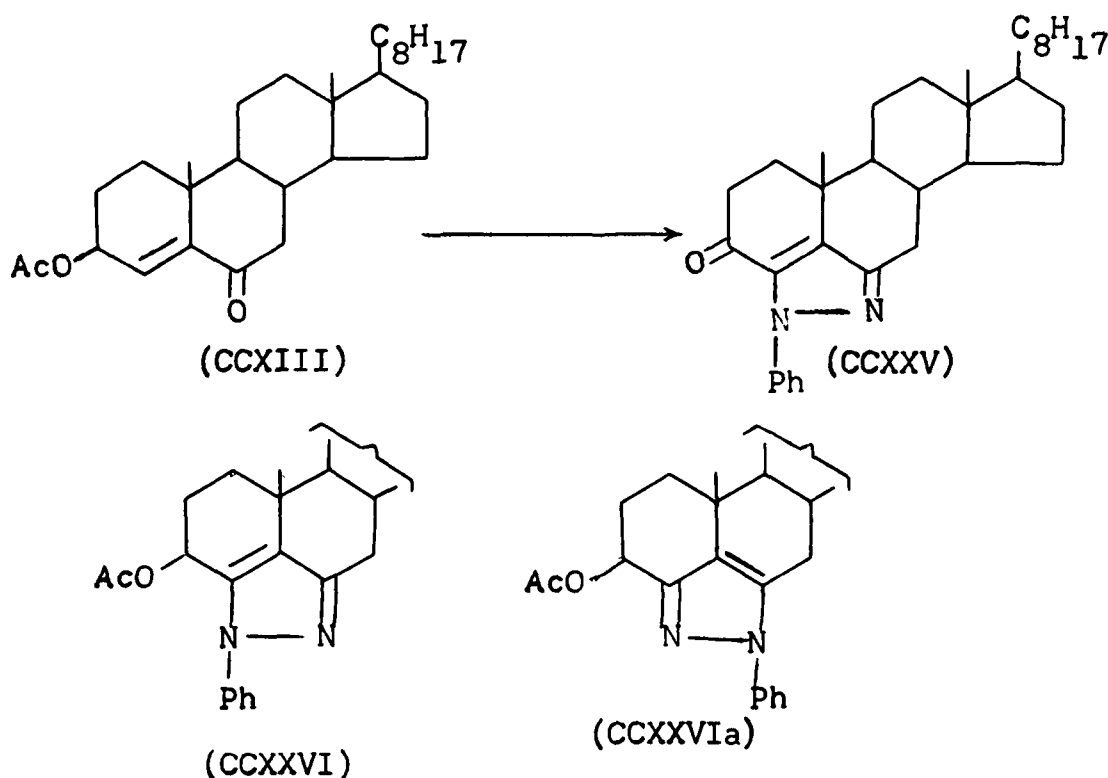


Thus the oil₂ obtained from the reaction of ketone (CCXII) with phenylhydrazine under nitrogen atmosphere can be characterized on the basis of spectral values and mechanistic consideration as 2'-phenyl-5-cholesteno[6,4-cd]-pyrazole (CCXXIII).

Reaction of 6-oxo-4-cholesten-3 β -yl acetate (CCXIII) with phenylhydrazine (under atmospheric conditions)

The ketone (CCXIII) was prepared according to the literature procedure¹¹⁴ [γ_{\max} 1730 ($\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$), 1685 ($-\text{C}=\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-$), 1625 ($-\text{C}=\text{C}-$), 1230 (acetate): δ 5.9 br, s (1H, C_4 -vinylic), 5.2 m (1H, C_3 - αH , $\text{W}_{1/2}=16$ Hz), 2.0 s (3H, $\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}$), 1.0, 0.9, 0.8 and 0.7 (methyl protons)]. The spectral values of the ketone were obtained for total identification and for comparison purposes.

The ketone (CCXIII)¹¹⁴ on treatment with phenylhydrazine under atmospheric conditions after usual work up and column chromatography gave a single compound, m.p. 226°.

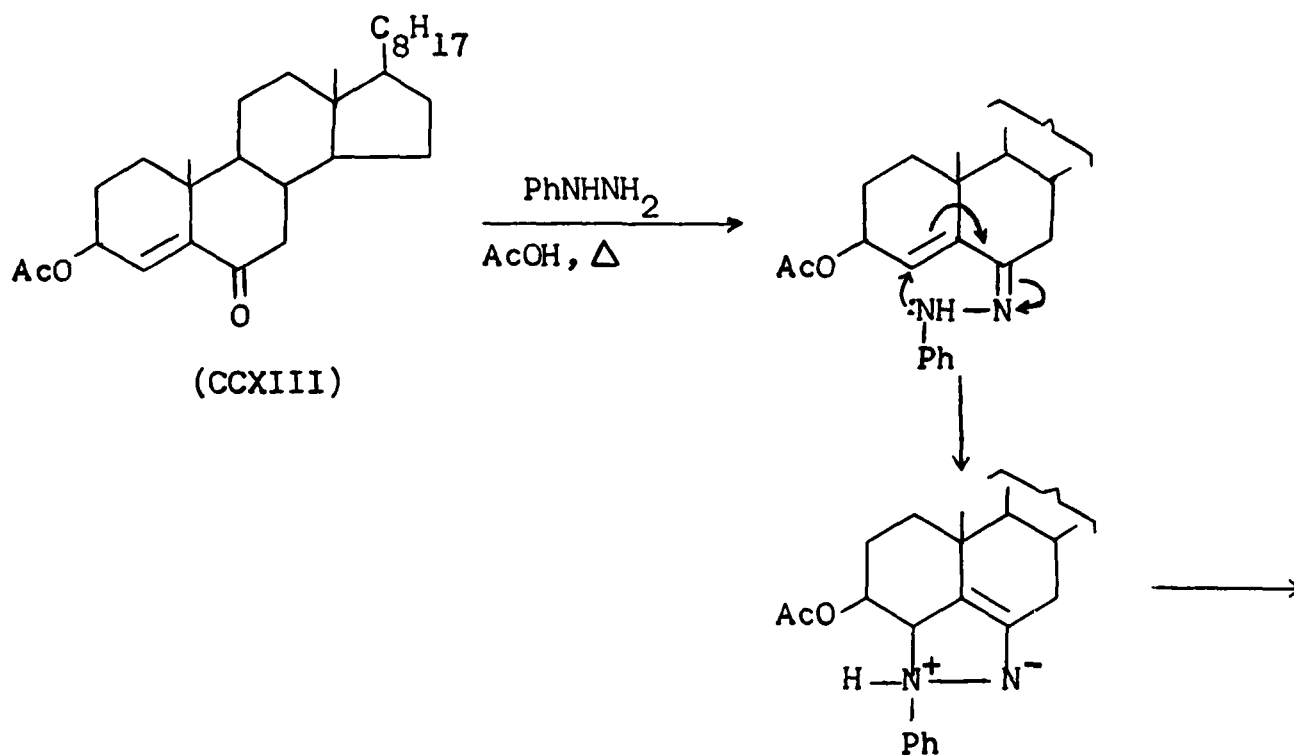


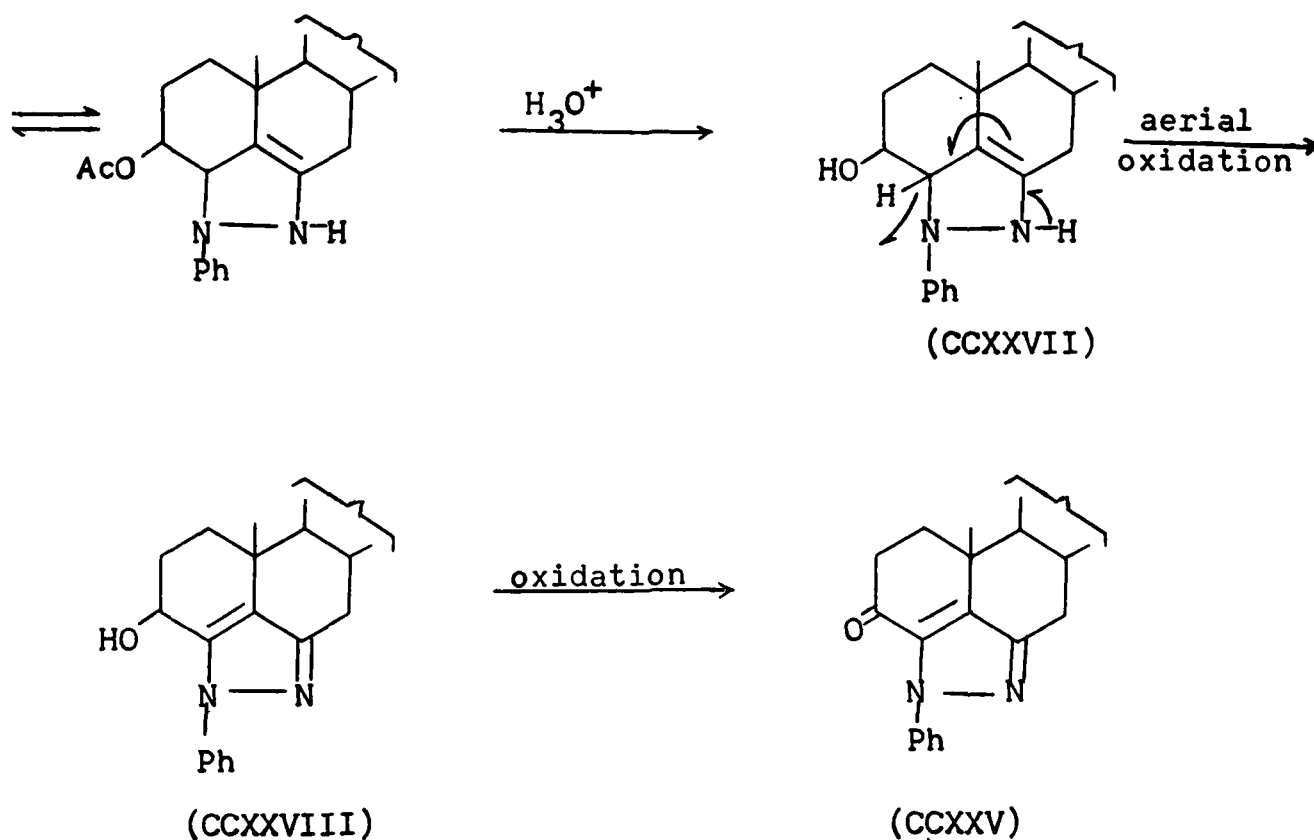
The compound m.p. 226° analysed for $C_{33}H_{46}N_2O$ and the mass spectrum gave molecular ion peak at m/z 486 ($C_{33}H_{46}N_2O$). This composition is intriguing since the expected structures (CCXXVI) and (CCXXVIa) require $C_{35}H_{50}N_2O_2$. It may be argued that the hydrolysis of the acetate function has occurred during the course of the reaction or chromatography. But in that case the composition of the hydroxypyrazole would be $C_{33}H_{48}N_2O$. This therefore suggested that the reaction has gone beyond the normal pyrazole formation and subsequent hydrolytic stage. The i.r. spectrum of the compound gave a very strong and informative band at 1680 cm^{-1} which indicated the presence of an α,β -unsaturated carbonyl chromophore as present in the starting ketone itself (CCXIII). The presence of two nitrogen atoms in the product shows that the reaction of the ketone (CCXIII) with phenylhydrazine has occurred. In all possibilities the original keto function at C_6 must have been involved in a routine manner leading to the corresponding phenylhydrazone. This then implies that a new α,β -unsaturated carbonyl chromophore has been generated during the course of the reaction to give a strong band at 1680 cm^{-1} . The other prominent features of i.r. are bands at 3050 w , 1600 s , 750 and 690 cm^{-1} characteristic of monosubstituted benzene observed in phenylpyrazole type derivatives^{44,109}. The other significant band is at 1490 for $C=N$ group^{109,115}. Its u.v. spectrum showed absorption maxima at 310 , 258 and 226 nm ^{44,110}. The n.m.r. spectrum gave a broad multiplet centred at δ 7.5 integrating for 5 protons which could be assigned to aromatic protons. The signals

at δ 2.3 and 2.75 as multiplets are ascribable to C_2-H_2 and C_7-H_2 respectively as in structure (CCXXV). The methyl protons were recorded at δ 1.2 ($C_{10}-Me$), 1.1, 0.8, 0.72 and 0.66.

The formation of the compound (CCXXV) can be shown according to the schemes 6 and 6A. It may be noted here that carbonyl group at C_3 may be derived at any stage during the course of the reaction from the acetate function. This finds support from the fact that the same compound (CCXXV) was also obtained from the reaction of the diketone (CCXIV) when subjected to the similar reaction conditions.

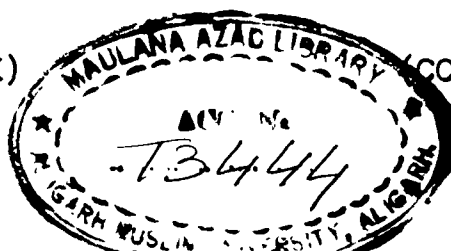
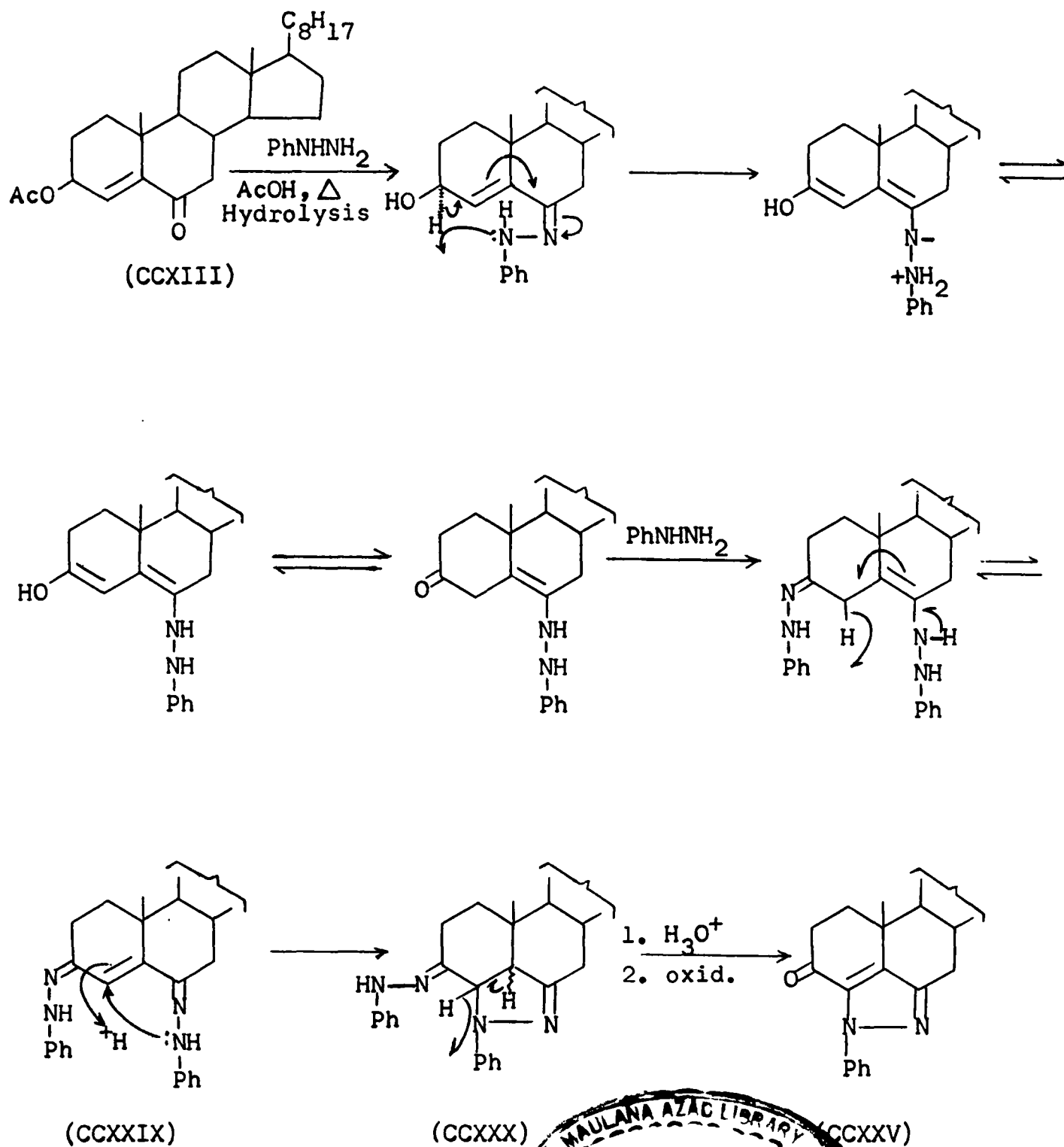
Scheme - 6





It is proposed that the aerial oxidation probably involving a free radical mechanism leads to the formation of the pyrazole (CCXXVIII) from the pyrazoline (CCXXVII) and the hydroxy group in the intermediate (CCXXVIII) being allylic undergoes ready oxidation leading to the formation of the α,β -unsaturated ketone as in (CCXXV). An alternate mechanism for the formation of the product (CCXXV) from the ketone (CCXIII) can also be suggested as in scheme-6A.

Scheme - 6A



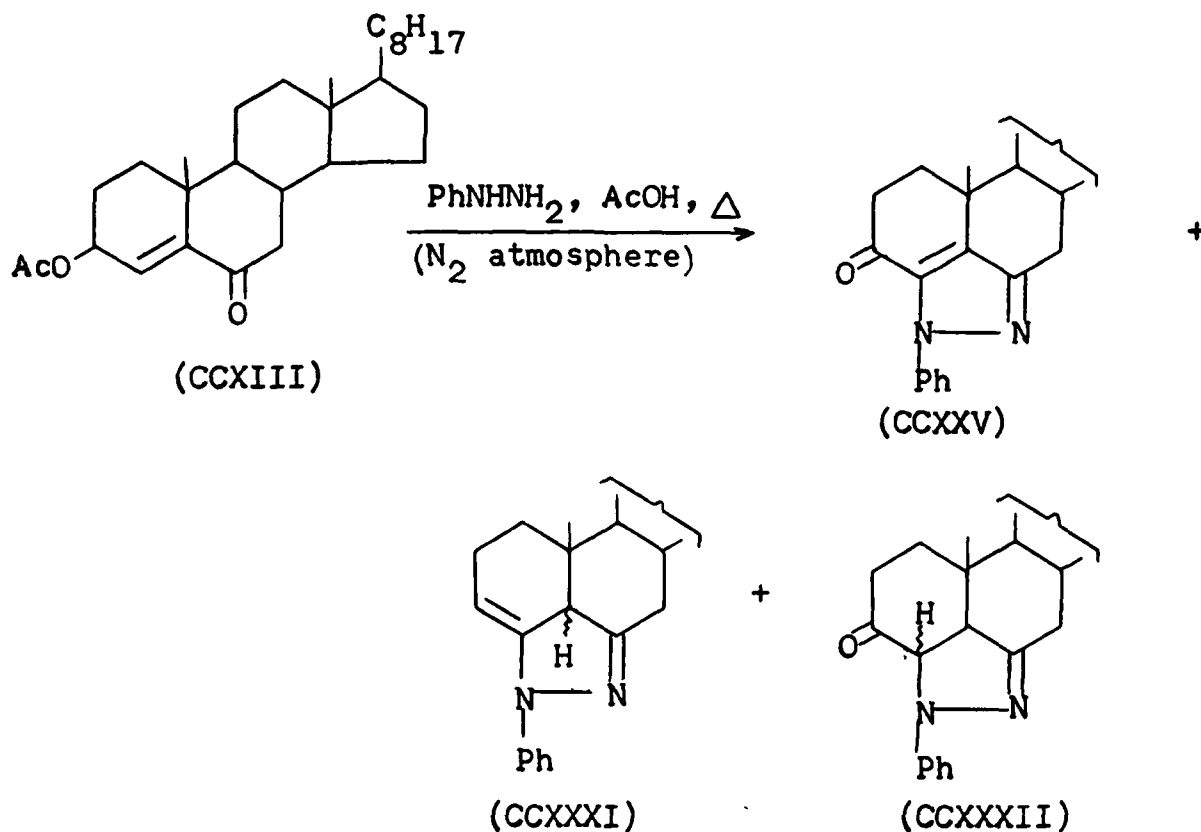
In this mechanism it is proposed that the intermediates (CCXXIX and CCXXX) lead to the formation of pyrazole (CCXXV), through bishydrazone formation followed by cyclization, hydrolysis and oxidation respectively. However, the intermediates (CCXXIX and CCXXX) were not isolated.

On the basis of molecular composition, spectral properties and mechanistic considerations the compound m.p.226° could best be characterized as 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV).

In order to have a better understanding of the reaction described above where atmospheric oxidation was involved, it was considered desirable to carry out the reaction under nitrogen. It was expected that the intermediate pyrazoline (CCXXXII) can be isolated, may be for a short period, by this procedure.

Reaction of 6-oxo-4-cholesten-3 β -yl acetate (CCXIII) with phenylhydrazine (under nitrogen)

The reaction of the ketone (CCXIII) with phenylhydrazine was carried out under nitrogen. After usual work up and column chromatography there were obtained three products. Two of them were obtained as non-crystallizable oils whereas the third was a solid m.p.226°.

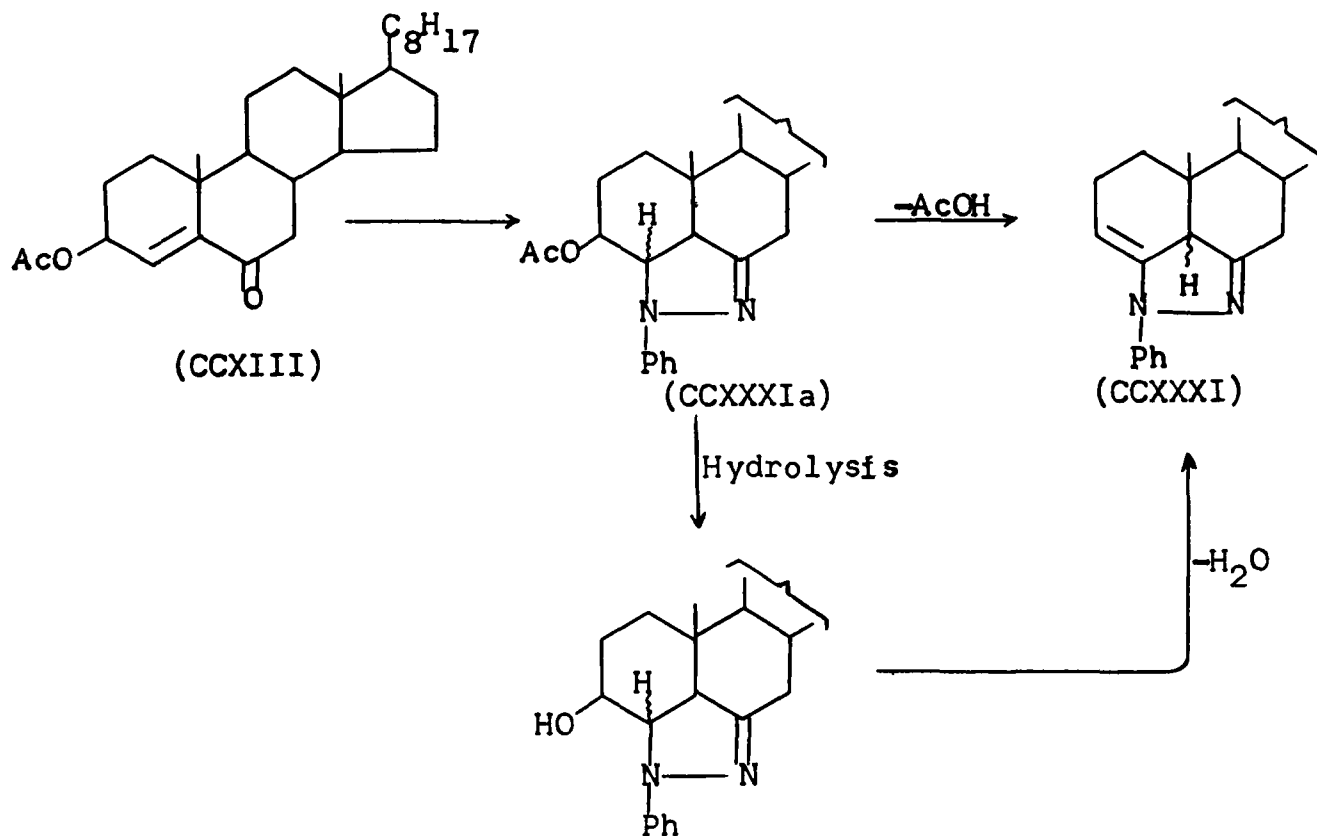


The solid compound m.p. 226° was found to be identical with (CCXXV) obtained in an earlier experiment (t.l.c., m.p., m.m.p., i.r., n.m.r. and mass).

Characterization of oil₁ as 2'-phenyl-3-cholesteno[4,6-cd]-pyrazoline (CCXXXI)

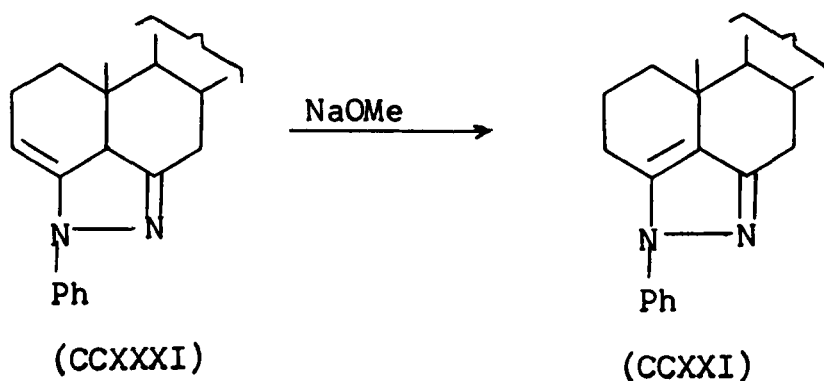
The oil₁ analysed for C₃₃H₄₈N₂. From the molecular composition alone the expected oxygen containing compounds (CCXXV and CCXXXII) can be discarded. The i.r. spectrum of the oil gave bands at 3040 w, 1620 s, 1590 s, 1480 s, 765 and 685 cm⁻¹. Mole-

cular composition and i.r. values are compatible with structure (CCXXXI). The n.m.r. spectrum gave a broad signal at δ 5.8 integrating for one proton which can be assigned to the C_3 -vinylic proton in structure (CCXXXI). The compound (CCXXXI) most likely arises by the overall expulsion of acetic acid from the expected pyrazoline (CCXXXIa). The acetic acid splits off as such during the course of the reaction or it may be lost in stages such as hydrolysis and loss of water.



The other signals in the n.m.r. spectrum were observed at δ 7.4 br,m (5H, C₆-H₅), 2.7 m (2H, C₇-H₂), 1.8 m (2H, C₂-H₂), 1.2 (C₁₀-Me), 1.1, 0.9, 0.8 and 0.7 (other methyl protons). These spectral values supported the structure (CCXXXI).

The compounds (CCXXXI) and (CCXXI) are double bond isomers and it was thought that the former can be isomerized to latter by usual acid or base treatments. Experimentally it was observed that (CCXXXI) isomerized to (CCXXI), m.p. and m.m.p. 152° through sodium methoxide. However, it should be reported that the isomerization did not occur with p-toluenesulphonic acid.



Thus on the basis of elemental analysis spectral values and chemical transformation oil₁ can be characterized as 2'-phenyl-3-cholesteno[4,6-cd]-pyrazoline (CCXXXI).

Characterization of oil₂ as 3-oxo-2'-phenyl-5~~6~~-cholestan[4,6-cd]-pyrazoline (CCXXXII)

The oil₂ was very unstable material for which only i.r. spectrum could be obtained as it was changing to (CCXXV) as revealed by t.l.c. The i.r. bands were observed at 3060 w, 1705 m, 1600 s, 1500 s, 750 m and 690 cm⁻¹. A strong band at 1705 cm⁻¹ suggested the presence of a non-conjugated ketone as in structure (CCXXXII). These data are compatible with the pyrazoline structure (CCXXXII). The compound (CCXXXII) on oxidation with leadtetraacetate gave (CCXXV) m.p. and m.m.p. 226°. The oil₂ can be characterized as 3-oxo-2'-phenyl-5~~6~~-cholestan[4,6-cd]-pyrazoline (CCXXXII).

It is to be noted that neither the acetoxy nor the hydroxy pyrazoline could be isolated. However, the formation of (CCXXXII) the precursor of (CCXXV), indicated that apparently hydrolysis of the acetate function followed by oxidation of allylic alcohol (CCXXVIII) has taken place concurrently as shown in scheme-7.

In subsequent work it was observed that as far as pyrazole or pyrazoline formation is concerned 4-en-6-one structure reacts well whereas, 4-en-3-one structure only gave the phenylhydrazone.

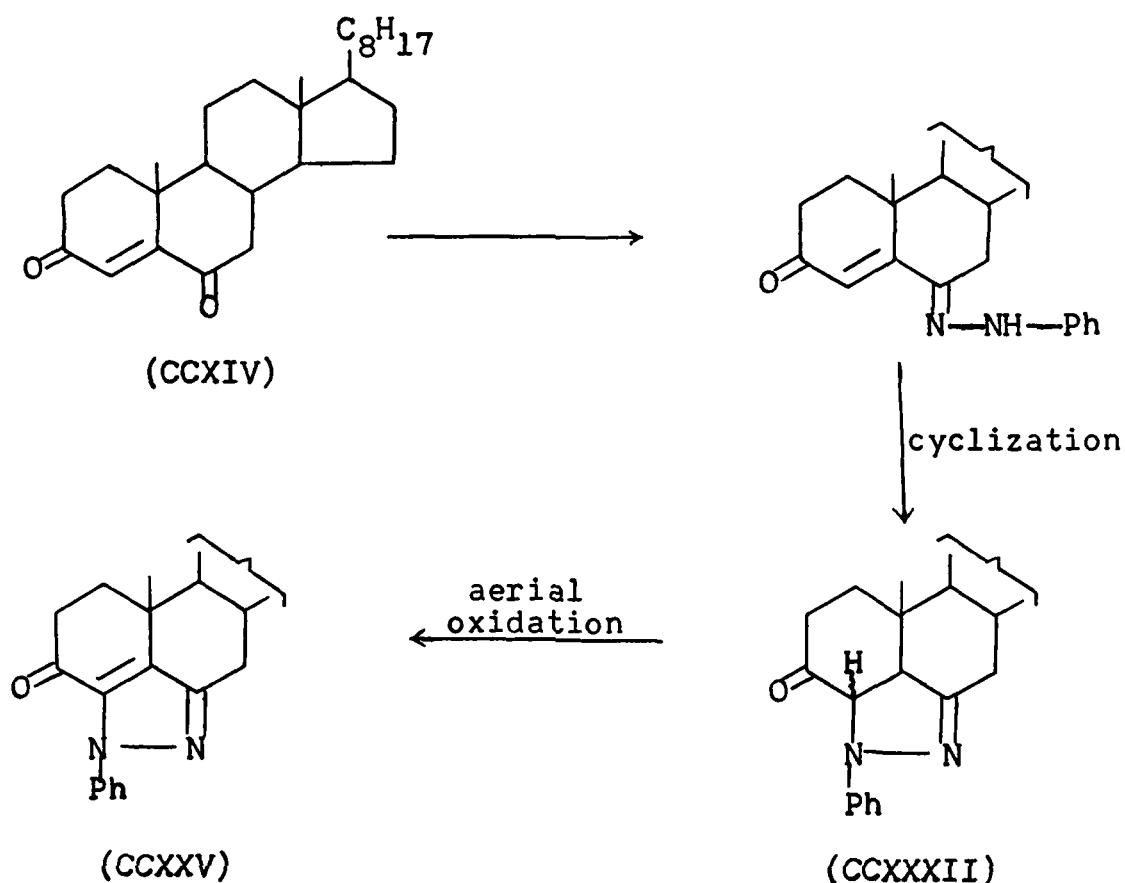
Reaction of 4-cholestene-3,6-dione (CCXIV) with phenylhydrazine

The ketone (CCXIV) was prepared according to the literature procedure¹¹⁶ [ν]_{max} 1680 (—C=C— $\overset{\text{O}}{\parallel}$ C—) and 1600 cm⁻¹ (C=C): δ 6.08 s

(1H, C₄-vinylic proton), 2.4 m (4H, C₂-H₂ and C₇-H₂), 1.2, 0.9, 0.85 and 0.7 (methyl protons).

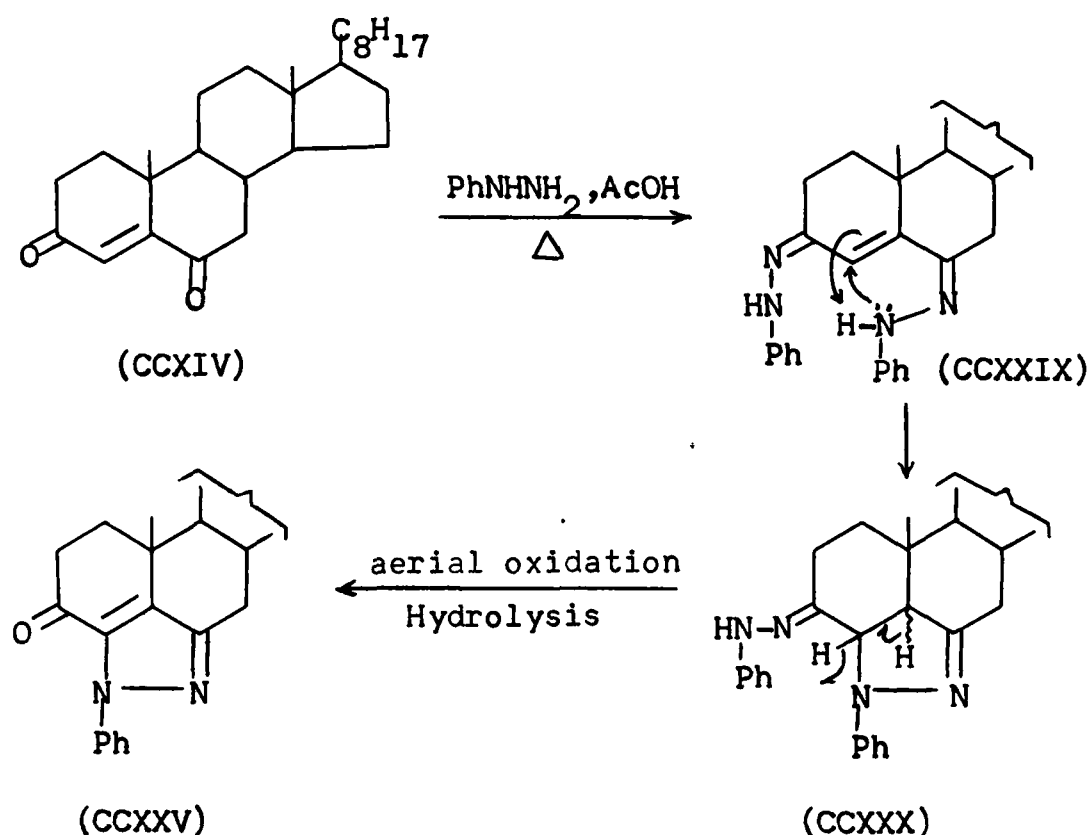
One of the possible pyrazoles obtained from the ketone (CCXIV) and phenylhydrazine could be (CCXXV), m.p.226°. Having this in mind the reaction of the ketone (CCXIV) was conducted with phenylhydrazine. After usual work up and column chromatography only one product was obtained having m.p.226°. This was found to be identical with (CCXXV). One of the possible ways to account for the formation of (CCXXV) in this reaction could be written as in scheme-7.

Scheme - 7



This mechanism involves the reaction of phenylhydrazine with C₆-ketofunction in preference to C₃-ketone which is in contrast to the general observation that a steroid C₃-ketone is more reactive than C₆-ketone, may be due to steric reasons. Alternatively, another mechanism can be written for the formation of (CCXXV) as in scheme-8.

Scheme - 8

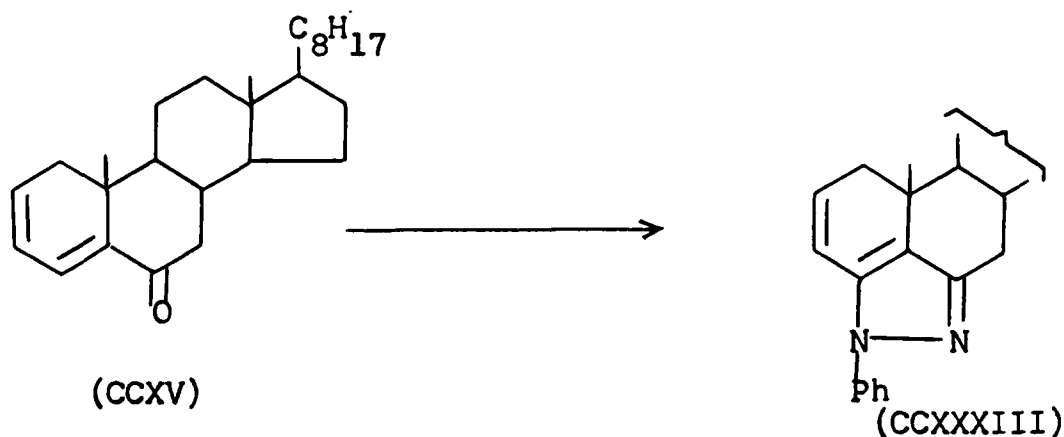


This mechanism involves the intermediacy of the bishydrazone (CCXXIX). This undergoes cyclization, hydrolysis/oxidation leading to (CCXXV).

Reaction of 2,4-cholestadien-6-one (CCXV) with phenylhydrazine

The ketone (CCXV) was prepared according to the literature procedure¹⁰⁸ $[\gamma]_{\max}$ 3120 (C=C-H), 1670 (-C=C-C-), 1625 (C=C): λ_{\max} 316 nm; δ 6.6 mc (1H, C₂-H), 5.96 dist. d (2H, C₃-H and C₄-H), 2.3 (2H, C₇-H₂), 1.0, 0.95, 0.88 and 0.70 (methyl protons).

The ketone (CCXV)¹⁰⁸ on reaction with phenylhydrazine in acetic acid afforded a single compound m.p.178°.



The compound m.p.178° analysed for C₃₃H₄₆N₂. The mass spectrum also supported this composition (M⁺ 470; C₃₃H₄₆N₂). The i.r. spectrum gave bands at 3060 w, 1600 s, 1500 s, 760 and 680 cm⁻¹ typical of phenylpyrazole derivatives⁴⁴. The n.m.r. signals were observed at δ 7.3 br,m (5H, C₆-H₅), 6.58 d (1H, C₃-H, J=9 Hz), 5.8 br,m (1H, C₂-H), 2.76 br,m (2H, C₇-H₂), 1.8 br,m (2H, C₁-H₂), 1.2, 1.05, 0.9, 0.83 and 0.75 (methyl protons). Its u.v. spectrum gave absorption maxima at 260 nm.

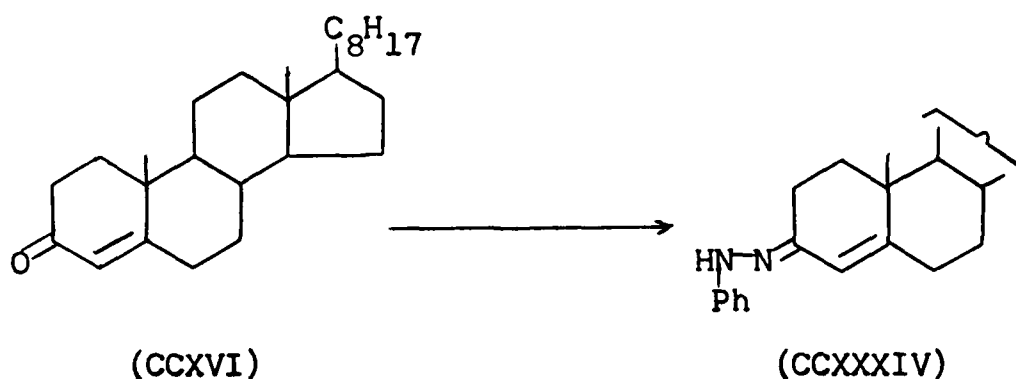
These spectral values are in accordance with the expected structure (CCXXXIII).

Reaction of 4-cholesten-3-one (CCXVI) with phenylhydrazine:

4-cholesten-3-one phenylhydrazone (CCXXXIV)

The ketone (CCXVI) was prepared according to the literature procedure¹¹⁷ [ν_{\max} 1680 ($-\text{C}=\text{C}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$), 1620 ($-\text{C}=\text{C}-$): δ 5.9 (1H, C_4-H), 2.2 br,m (2H, C_2-H_2), 1.9 br,m (2H, C_6-H_2), 1.01, 0.9, 0.8 and 0.7 (methyl protons), λ_{\max} 240 nm.

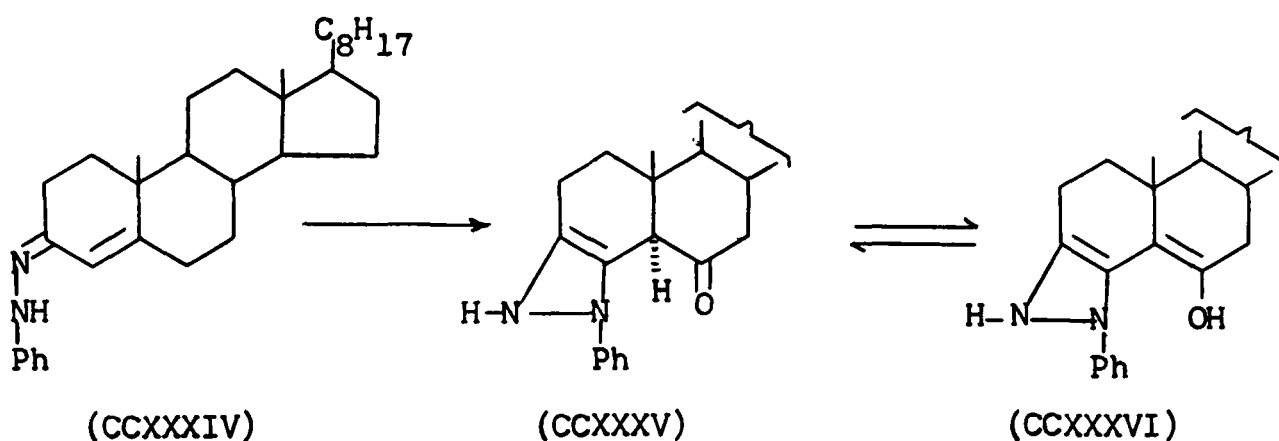
The reaction of 4-cholesten-3-one (CCXVI)¹¹⁷ with phenylhydrazine provided after usual work up a single compound m.p.144°.



The compound m.p.144°, analysed for $\text{C}_{33}\text{H}_{50}\text{N}_2$ and showed in its i.r. spectrum bands at 3420-3330 br (NH-Ph), 3030, 1600 s (aromatic), 1590 and 1495 cm^{-1} (C=N vibrations)¹⁰⁹. It showed no band for carbonyl group. In addition to bands typical of phenyl

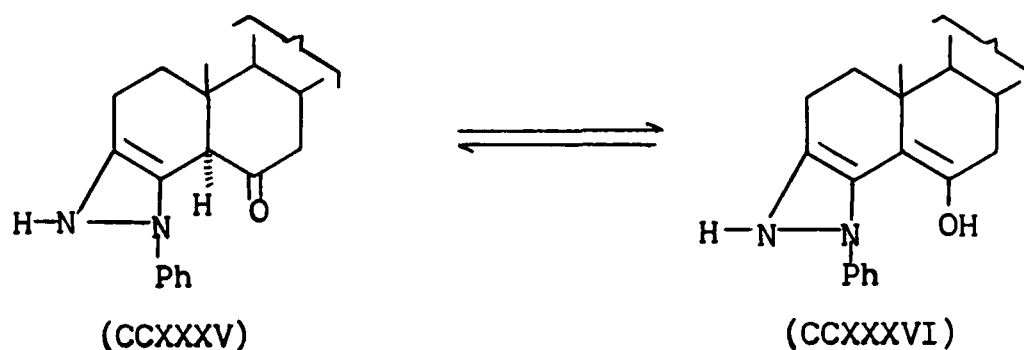
ring and C=N, the spectrum revealed the presence of N-H band at $3330-3420\text{ cm}^{-1}$, which hinted that the compound is a phenylhydrazone and not the expected pyrazole or pyrazoline. The n.m.r. spectrum gave broad multiplet at δ 7.2 integrating for six protons, five aromatic and N-H¹¹⁰. A singlet was observed at δ 6.3 which may be assigned to C₄-vinylic proton as in structure (CCXXXIV). Other signals were observed at δ 2.3 br,m (2H, C₂-H₂), 1.1, 0.96, 0.83, 0.78 and 0.72 (methyl protons). On the basis of these spectral values the compound m.p.144° can be characterized as 4-cholesten-3-one phenylhydrazone (CCXXXIV).

Reaction of 4-cholesten-3-one phenylhydrazone (CCXXXIV) with acetic acid



The phenylhydrazone (CCXXXIV) was heated under reflux with acetic acid for two hours. After usual work up and column chromatography a compound m.p.185° was obtained.

The examination of the spectral data of the compound, m.p.185° revealed that doubly unsaturated five membered pyrazole moiety has not been formed as in the other reactions. Though Δ^4 -3 ketone moiety is necessary for the formation of pyrazole, but C₅-position happens to be tetrasubstituted, which perhaps prevents the formation of a pyrazole. In addition, the α,β -unsaturated system should have a β -hydrogen to facilitate the pyrazole formation. This left us to look at it otherwise, and the characterization was considered in the light of elemental analysis and spectral values.

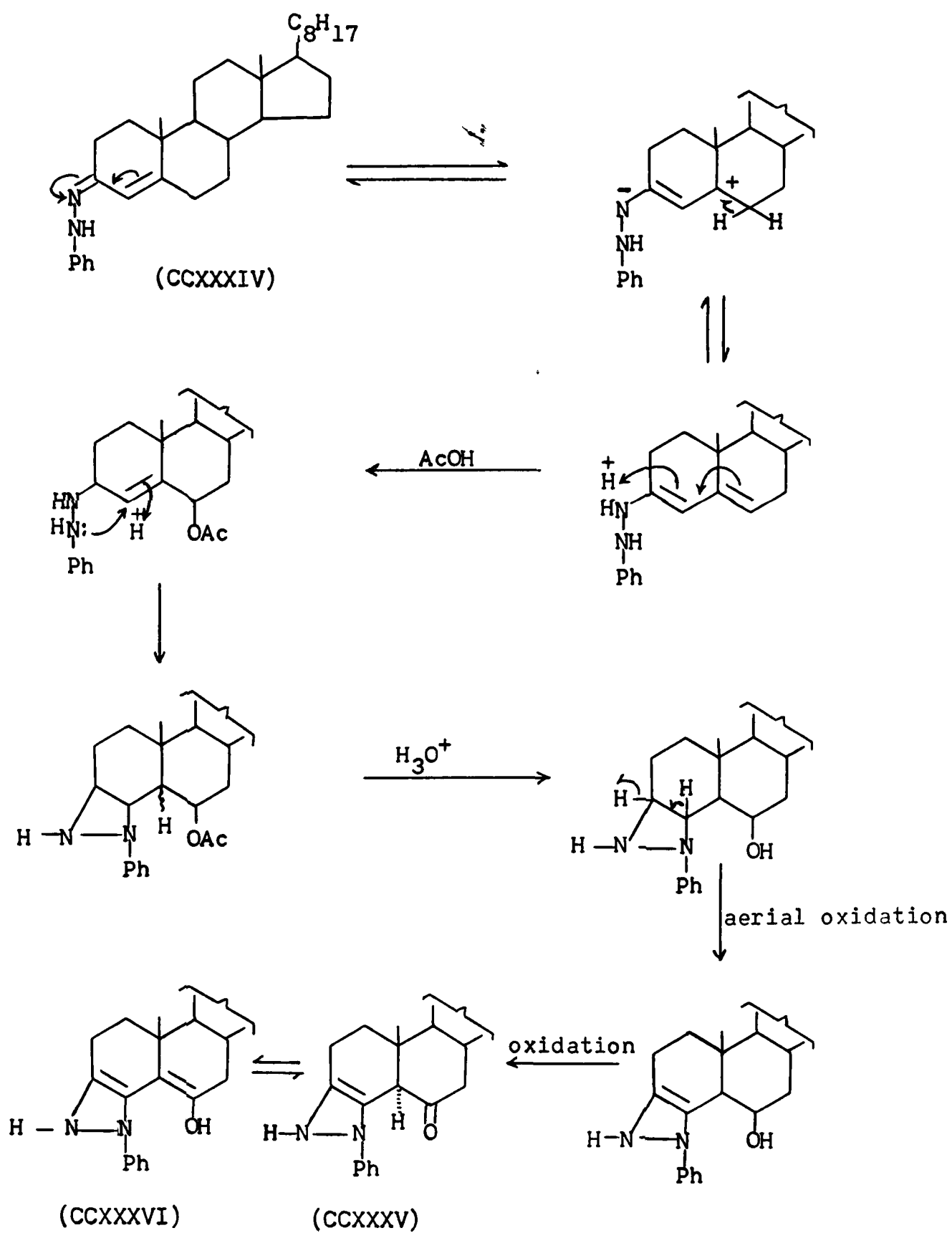


The compound m.p.185° analysed for C₃₃H₄₈N₂O. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 488 (C₃₃H₄₈N₂O). Molecular composition shows the presence of two nitrogens and one oxygen which indicated that the reaction of phenylhydrazine has occurred alongwith oxidation during the course of the reaction.

The i.r. spectrum of the compound gave a broad band at 3260 cm^{-1} which may be due to N-H stretching. A sharp band at 1710 cm^{-1} characteristic of isolated carbonyl group was also observed. Other bands were found at 1650, 1530 and 1460 cm^{-1} . The band at 3260 cm^{-1} signifies the presence of N-H¹⁰⁹ which supports the structure (CCXXXV). The n.m.r. spectrum of the compound exhibited a singlet at δ 9.9 which may be assigned to N-H proton¹¹⁸. A broad multiplet at δ 7.4 was observed for five aromatic protons. A singlet at δ 3.7 integrating for one proton may be assigned to $\text{C}_5\text{-}\alpha\text{H}$. A doublet centred at δ 2.7 ($J=10\text{ Hz}$) could be attributed to $\text{C}_7\text{-H}_2$. Other signals were observed at δ 1.2 ($\text{C}_{10}\text{-Me}$), 1.1, 0.9, 0.8 and 0.65 (other methyl protons). The i.r. and n.m.r. values are in good agreement with structure (CCXXXV). But the presence of a weak broad band in its i.r. spectrum at $3400\text{--}3500\text{ cm}^{-1}$ suggests that the compound (CCXXXV) may be in equilibrium with its enolic structure (CCXXXVI). Thus on the basis of the elemental analysis and spectral data the compound m.p. 185° could best be assigned the structure (CCXXXV) as 6-oxo- 5α -3-cholesteno[3,4]-N,N-phenylhydrazine.

The mechanism for the formation of the compound (CCXXXV) from the phenylhydrazone (CCXXXIV) can be shown as in scheme-9.

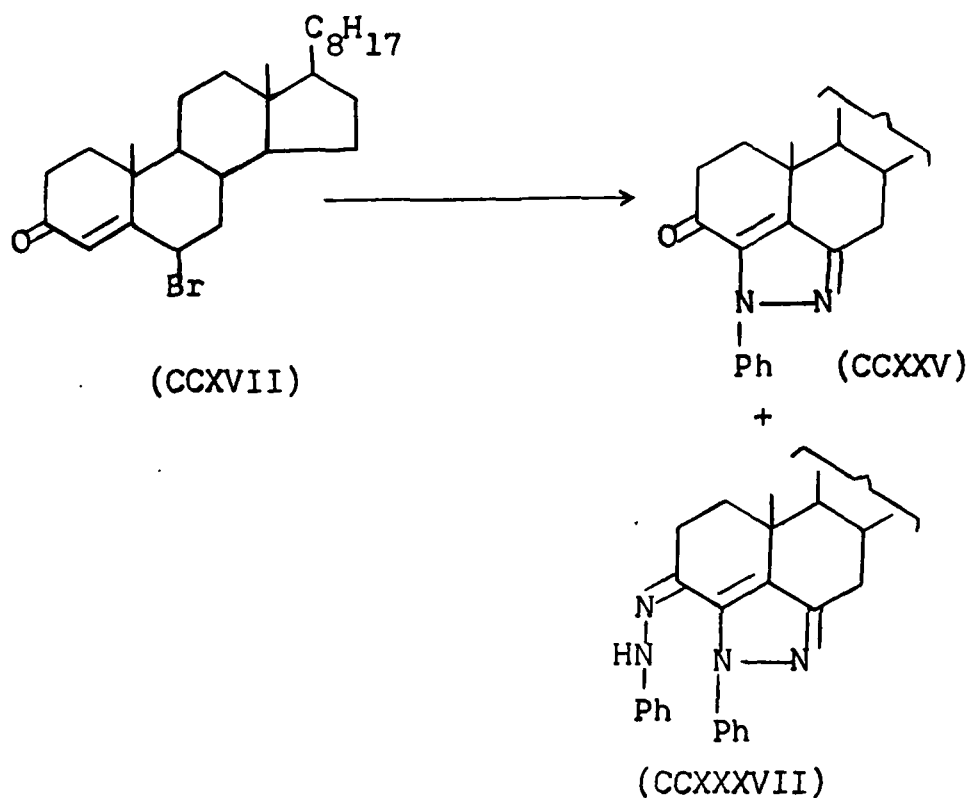
Scheme - 9



Reaction of 6 β -bromo-4-cholesten-3-one (CCXVII) with phenylhydrazine in acetic acid

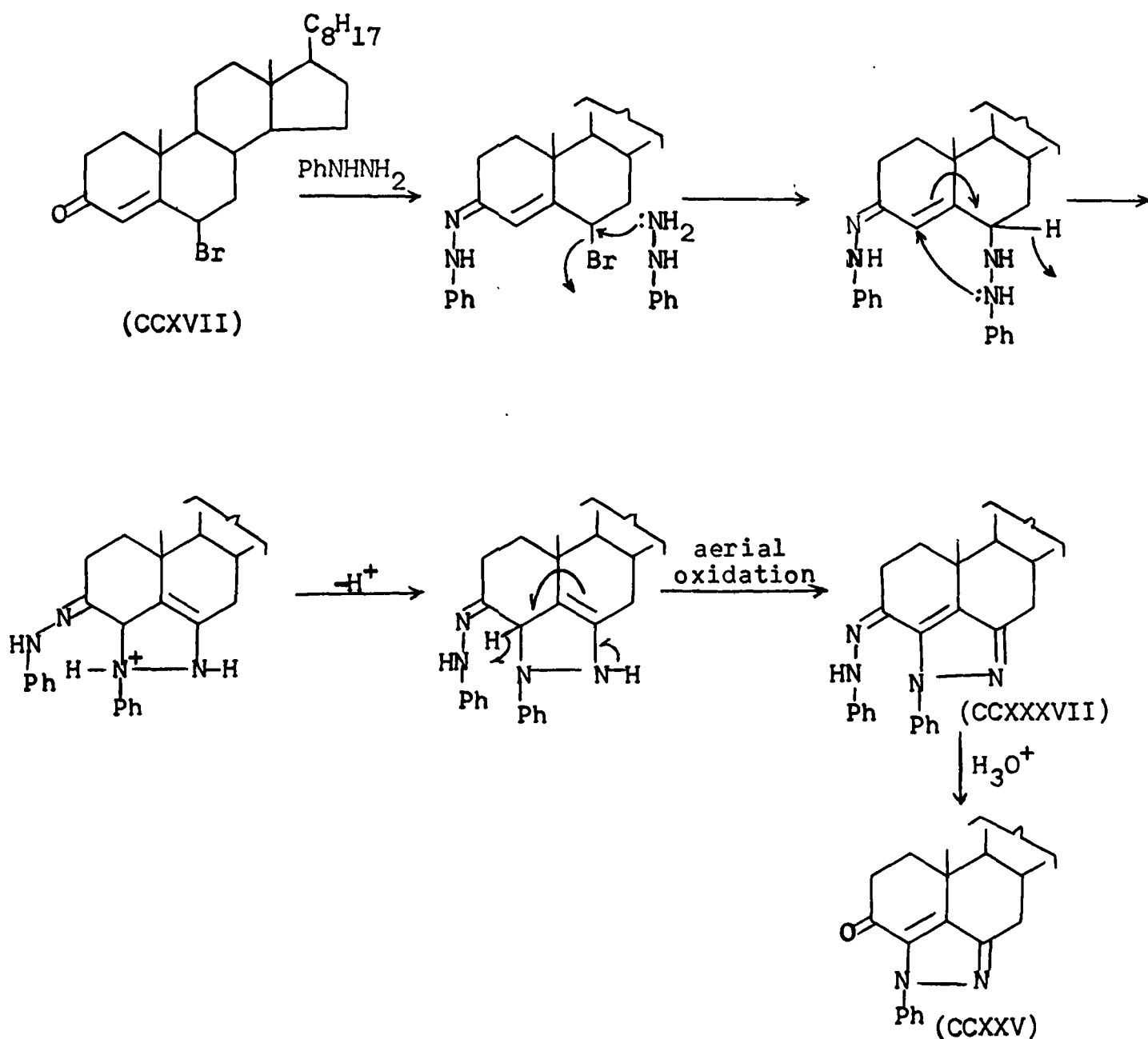
The ketone (CCXVII) was prepared according to the procedure described in literature^{117a} [ν_{\max} 1680 (C=C-C(=O)-), 1620 (C=C) and 740 cm^{-1} (C-Br): δ 5.8 s (1H, C₄-vinylic H), 4.9 m (1H, C₆- α H, W_{1/2}=7 Hz), 2.8 br (2H, C₂-H₂), 1.2, 0.91, 0.83 and 0.8 (methyl protons)].

The ketone (CCXVII)^{117a} on treatment with phenylhydrazine afforded, after usual work up and column chromatography, two compounds m.p. 226° and 195°. Both the compounds gave negative Beilstein test.



The compound m.p. 226° was found to be identical in all respects (t.l.c., m.p., m.m.p., i.r., n.m.r.) with (CCXXV) obtained earlier from the reaction of ketones (CCXIII) and (CCXIV). Formation of the compound (CCXXV) from the ketone (CCXVII) may be shown according to scheme-10.

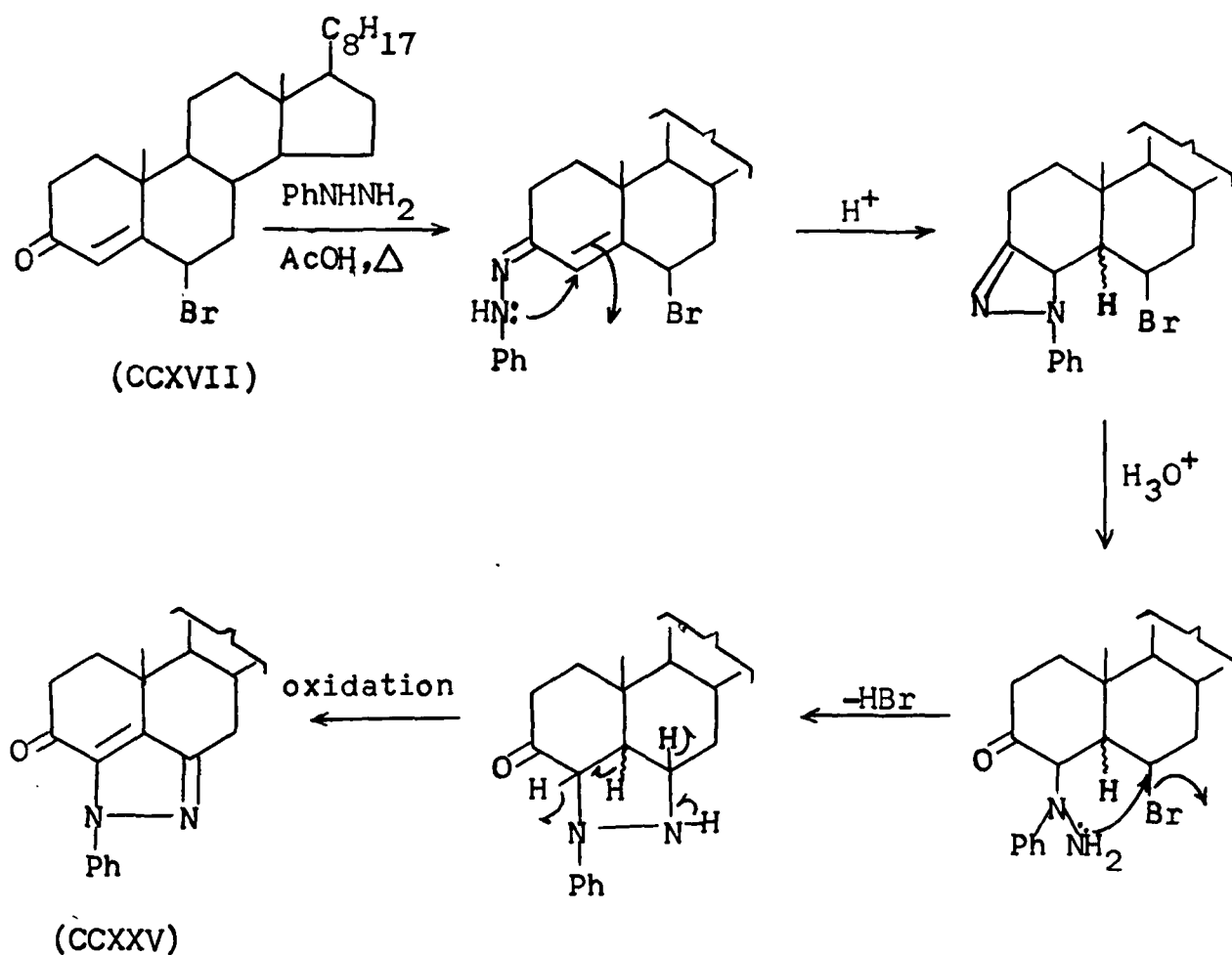
Scheme - 10



First step is the formation of the corresponding phenylhydrazone; another molecule of phenylhydrazine attacks at C₆ as a nucleophile, replacing bromine. Intramolecular reaction, oxidation, followed by hydrolysis resulted in the formation of the compound (CCXXV).

An alternate mechanism could also be suggested for the formation of (CCXXV) as shown in scheme-10A.

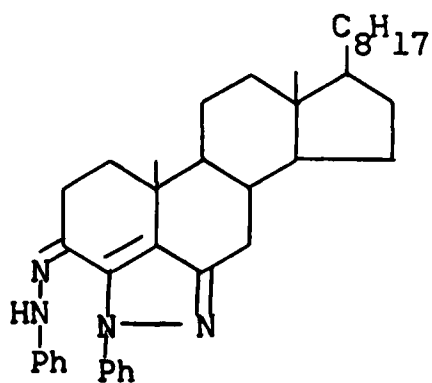
Scheme - 10A



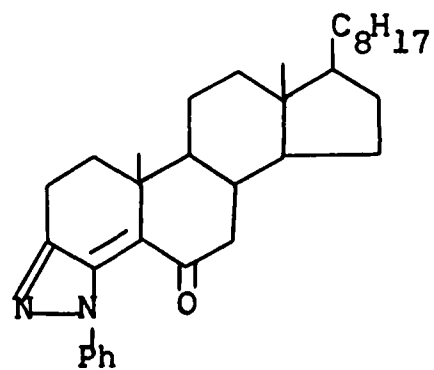
Characterization of the compound m.p.195° as 2'-phenyl-4-cholesteno
[4,6-cd]-pyrazole-3-one phenylhydrazone (CCXXXVII)

The compound m.p.195° analysed for $C_{39}H_{52}N_4$. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 576 ($C_{39}H_{52}N_4$).

The i.r. spectrum of the compound gave a weak band at 3240 cm^{-1} which can be ascribed to N-H vibrations^{109,110}, indicating it to be a phenylhydrazone moiety ($\text{Ph}-\text{NH}-\text{N}=\text{C}-$). The other bands in i.r. spectrum were observed at 1605, 750 and 695 cm^{-1} characteristic of monosubstituted benzene. Two prominent bands at 1590 and 1480 cm^{-1} can be assigned to C=N vibrations. Its u.v. spectrum gave absorption maxima at (λ_{max}) 274 and 365 nm ¹¹⁹. The n.m.r. spectrum of the compound exhibited a broad multiplet at δ 7.1-7.5 integrating for ten protons, which was assigned to the aromatic protons of the two phenyl groups. A singlet at δ 12.7 can be assigned to N-H proton of phenylhydrazone. The other features of n.m.r. spectrum are signals at δ 2.9 m (2H, C_2-H_2), 2.25 d ($J=10\text{ Hz}$, 2H, C_7-H_2), 1.2, 0.9, 0.8 and 0.73 (methyl protons). The above discussed i.r. and n.m.r. values alongwith the elemental analysis ($C_{39}H_{52}N_4$) suggested the reaction of two molecules of phenylhydrazine with the ketone (CCXVII). We may write two possible structures (CCXXXVII) and (CCXXXVIII) for the compound m.p.195°.



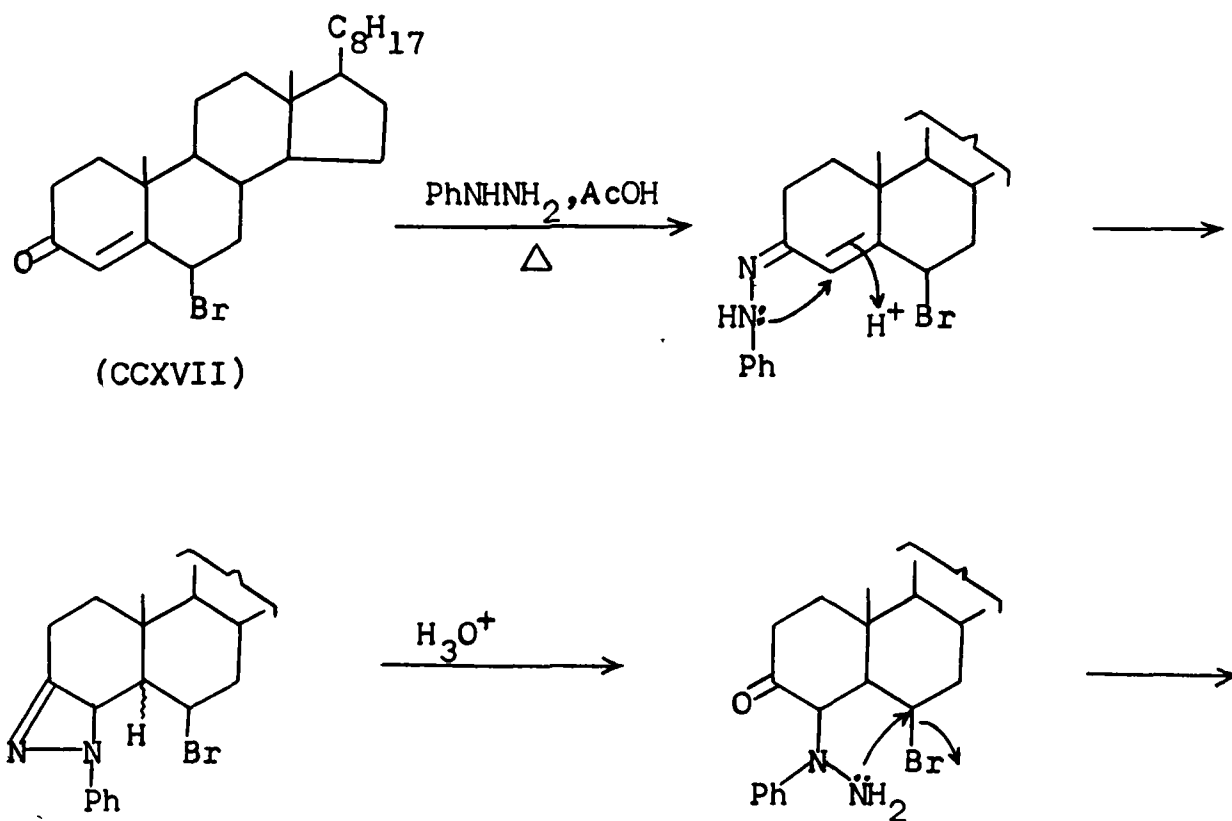
(CCXXXVII)



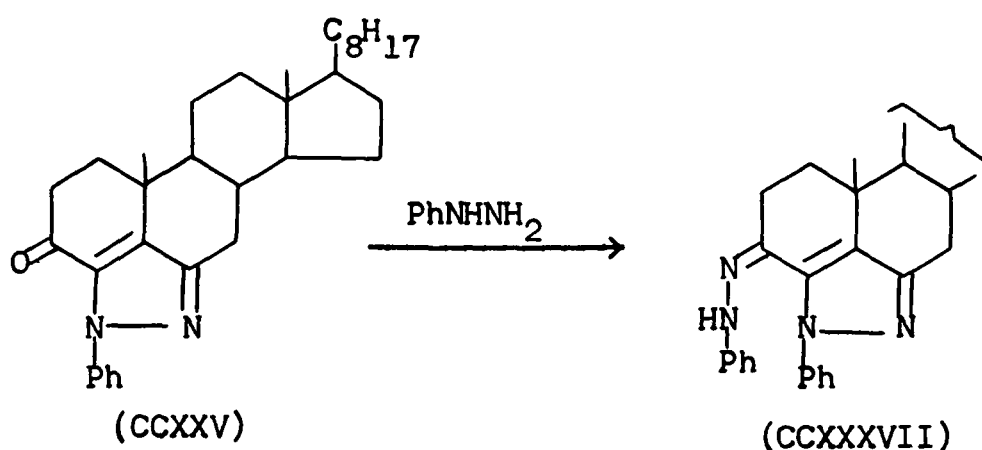
(CCXXXVIII)

On the basis of spectral values no clear distinction between (CCXXXVII) and (CCXXXVIII) was possible. Mechanistically both the structures are possible as shown in scheme-11 and 12.

Scheme - 11



The structure (CCXXXVII) is preferred over its isomer (CCXXXVIII) on the basis that the compound m.p.195° was obtained from (CCXXV) by the reaction with phenylhydrazine under mild conditions.

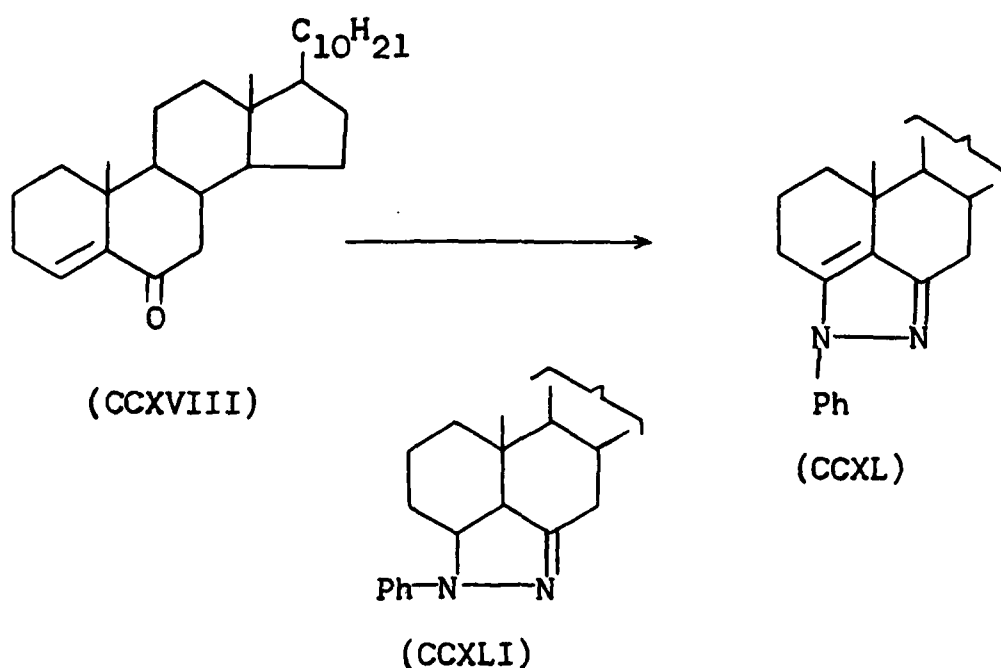


Thus on the basis of elemental analysis, spectral values and chemical evidence the compound m.p.195° can be characterized as 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole-3-one phenylhydrazone (CCXXXVII).

In order to assess the consistency of the reaction between steroidal α,β -unsaturated ketones and phenylhydrazine leading to pyrazoles, it was considered desirable to extend this study onto the stigmastane series.

Reaction of 4-stigmasten-6-one (CCXVIII) with phenylhydrazine

The ketone (CCXVIII) on reaction with phenylhydrazine afforded after usual work up and column chromatography a single compound m.p.132°.



The compound m.p.132° analysed for $C_{35}H_{52}N_2$. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 500 ($C_{35}H_{52}N_2$). The mass spectrum discarded pyrazoline structure (CCXLI). The i.r. spectrum of the compound gave bands at 3015 w, 1600 s, 1500, 760 and 690 cm^{-1} (characteristic of phenylpyrazole moiety)^{44,109,115} as in structure (CCXL). The n.m.r. signals were recorded at δ 7.47 br,m (5H, C_6H_5), 2.83 br,m

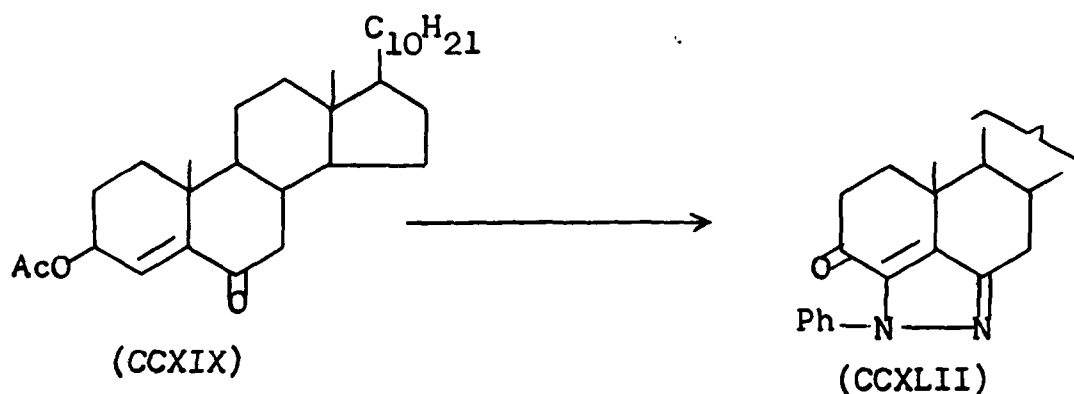
(2H, C₇-H₂), 2.0 br,m (2H, C₃-H₂), 1.2, 1.1, 0.9 and 0.7 (methyl protons). Its u.v. spectrum gave absorption maxima at 260 nm.

In analogy with the earlier observations in the cholestane series and on the basis of the spectral properties the compound m.p.132° can be characterized as 2'-phenyl-4-stigmasteno [4,6-cd]-pyrazole (CCXL).

The formation of the compound (CCXL) from (CCXVIII) under the conditions can be described as shown earlier in the scheme-4.

Reaction of 6-oxo-4-stigmasten-3β-yl acetate (CCXIX) with phenylhydrazine

The ketone (CCXIX) on reaction with phenylhydrazine under the conditions described above afforded a single compound m.p.147°.

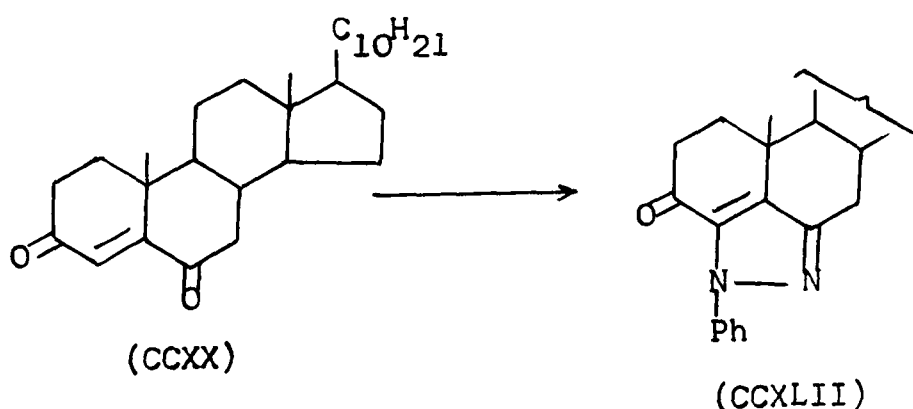


The compound m.p.147° analysed for C₃₅H₅₀N₂O. The composition was further supported by its mass spectrum which gave mole-

cular ion peak at m/z 514. The i.r. spectrum of the compound gave bands at 1680 s ($\text{CH}=\text{C}-\overset{\text{O}}{\parallel}\text{C}-$), 3020 w, 1600 w, 1500, 760 and 690 cm^{-1} (phenylpyrazole moiety). The n.m.r. signals were observed at δ 7.5 br,m (5H, C_6-H_5), 2.83 br,m (2H, C_7-H_2), 2.5 br,m (2H, C_2-H_2), 1.2, 1.1, 0.9 and 0.7 (methyl protons). Its u.v. spectrum gave absorption maxima at 260 and 285 nm. The spectral values supported structure (CCXLII).

In analogy with the results obtained in the cholestane series and on the basis of spectral values and elemental analysis the compound m.p. 147° can best be characterized as 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII).

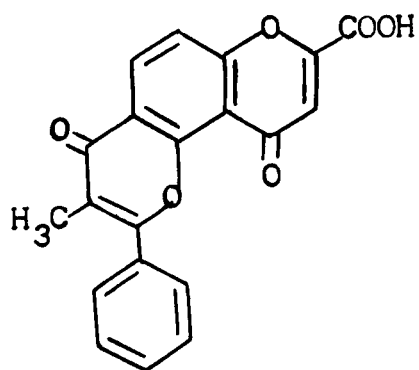
Reaction of 4-stigmastene-3,6-dione (CCXX) with phenylhydrazine



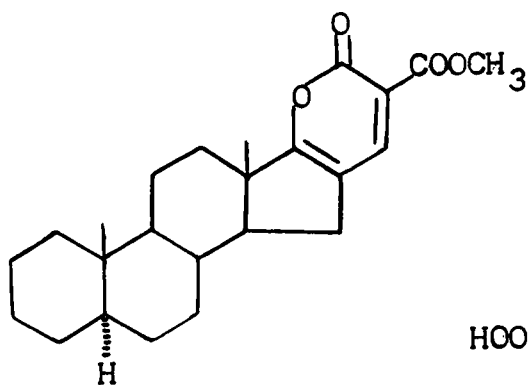
The ketone (CCXX) when treated with phenylhydrazine under similar conditions afforded a single compound m.p. 147° . This compound m.p. 147° was found to be identical in all respects with the compound 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII) [t.l.c., m.p., m.m.p., i.r., n.m.r. and mass].

STEROIDAL PYRANS

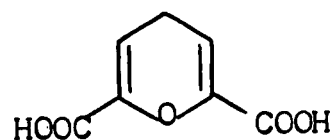
The presence of pyran moiety in various organic compounds induces biological potentials^{50a,b}. 4,10-Dioxo-3-methyl-2-phenyl-4H,10H-benzo[1,2-b:3,4-b']-dipyrans-8-carboxylic acid (CCXLIII)¹²⁰ shows high antiallergic activity and many naturally occurring pyrones, such as 5 α -androstand[16,17-e]-3'-carbomethoxy-2'-pyrone (CLI)⁸⁵ exhibited cytotoxicity and/or antitumor activity. Prompted by the results obtained, many workers reported the synthesis of pyrans. Synthesis of γ -pyran-2,6-dicarboxylic acid (XCVII) and 2-methyl-6-acetyl- Δ^2 -dihydropyran (CIX) was subsequently reported.^{51,60} Groot and Jansen⁷⁸ reported the simple and one step synthesis of 2H-pyrans. Many other workers reported the synthesis of pyrans, dihydropyrans and pyrones⁵¹⁻⁸⁵ and some of them reported their biological potentials, but very little has been mentioned about the synthesis of steroidal pyrans. Hence with a view of synthesizing pyrans in the steroidal systems we carried out the reactions of some of the easily accessible α,β -unsaturated ketones in the cholestane series with ethylacetoacetate in the presence of zinc chloride, acetic acid and acetic anhydride. The ketones selected for the present study are 4-cholestene-3,6-dione (CCXIV), 4-cholesten-3-one (CCXVI), 6 β -bromo-4-cholesten-3-one (CCXVII), 4,6-cholestadien-3-one (CCXLIV), 4-cholesten-6-one (CCXII), 3,5-cholestadien-7-one (CCIX) and 7-oxo-5-cholesten-3 β -yl acetate (CCXLV). For the sake of convenience, structures of some of the ketones have been reproduced here.



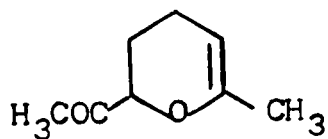
(CCXLIII)



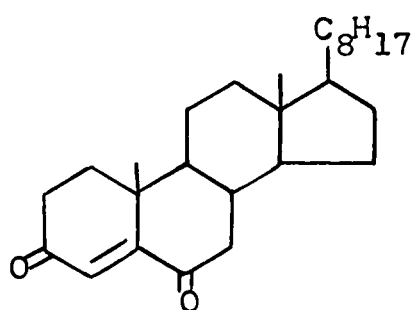
(CLI)



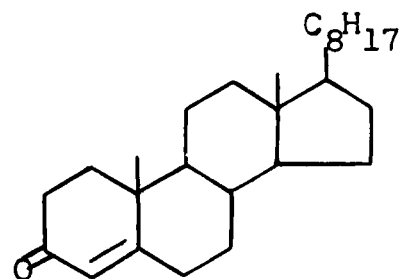
(XCVII)



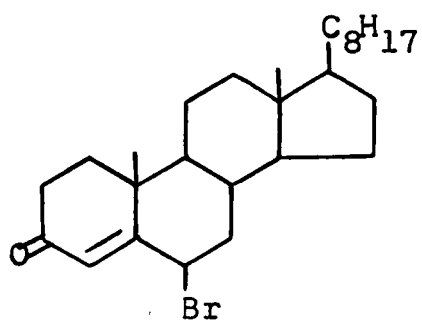
(CIX)



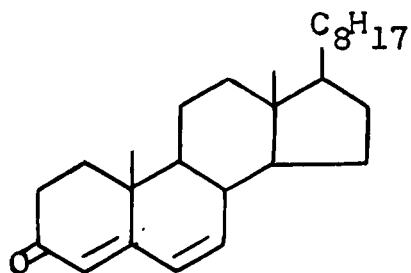
(CCXIV)



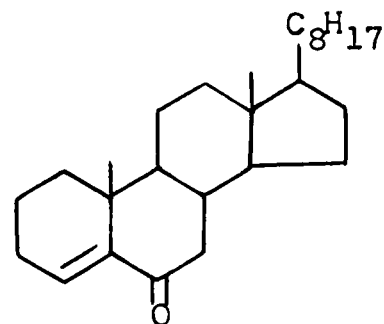
(CCXVI)



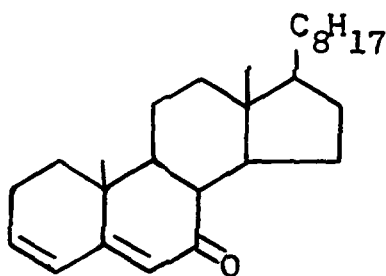
(CCXVII)



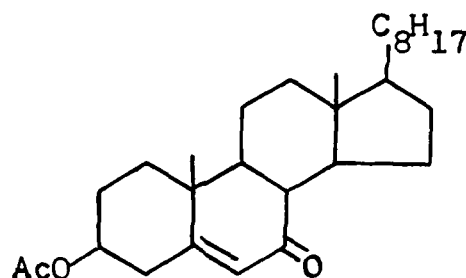
(CCXLIV)



(CCXII)



(CCIX)

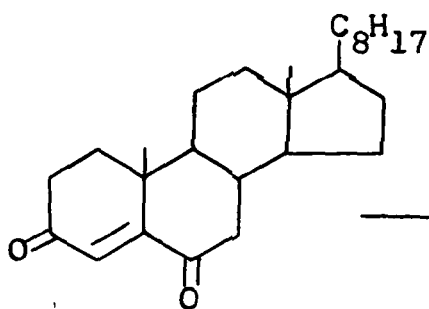


(CCXLV)

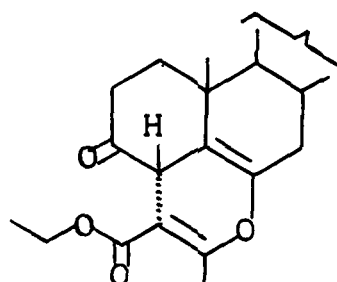
The structures of the products were established on the basis of elemental analysis, i.r., n.m.r., u.v. and in some cases by mass spectrometry.

Reaction of 4-cholestene-3,6-dione (CCXIV) with ethylacetoacetate in the presence of zinc chloride (fused), acetic acid and acetic anhydride

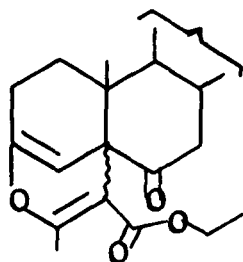
The ketone (CCXIV)¹¹⁶ on reaction with ethylacetoacetate after usual work up and column chromatography afforded a single compound m.p.147°.



(CCXIV)



(CCXLVI)



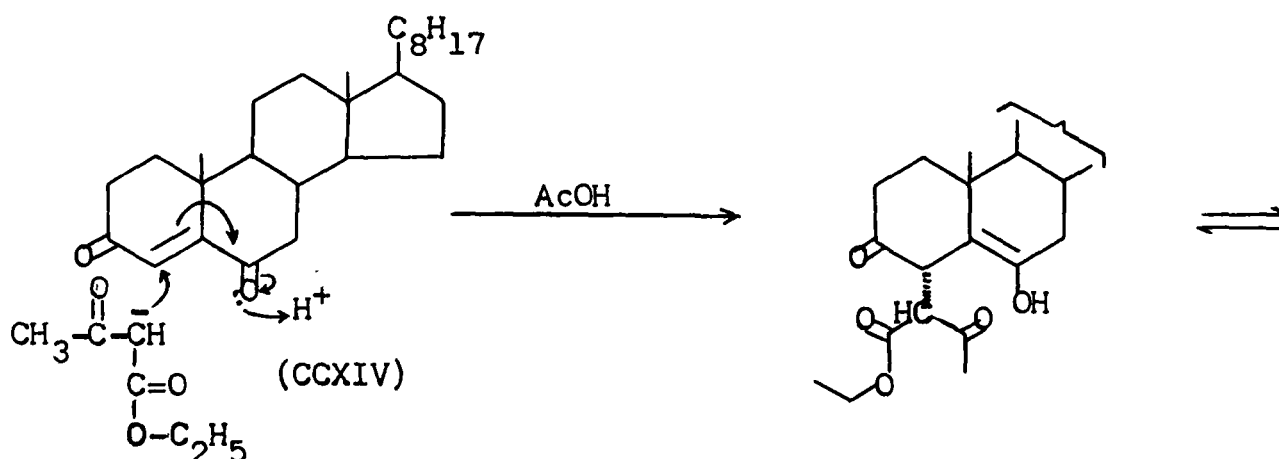
(CCXLVIa)

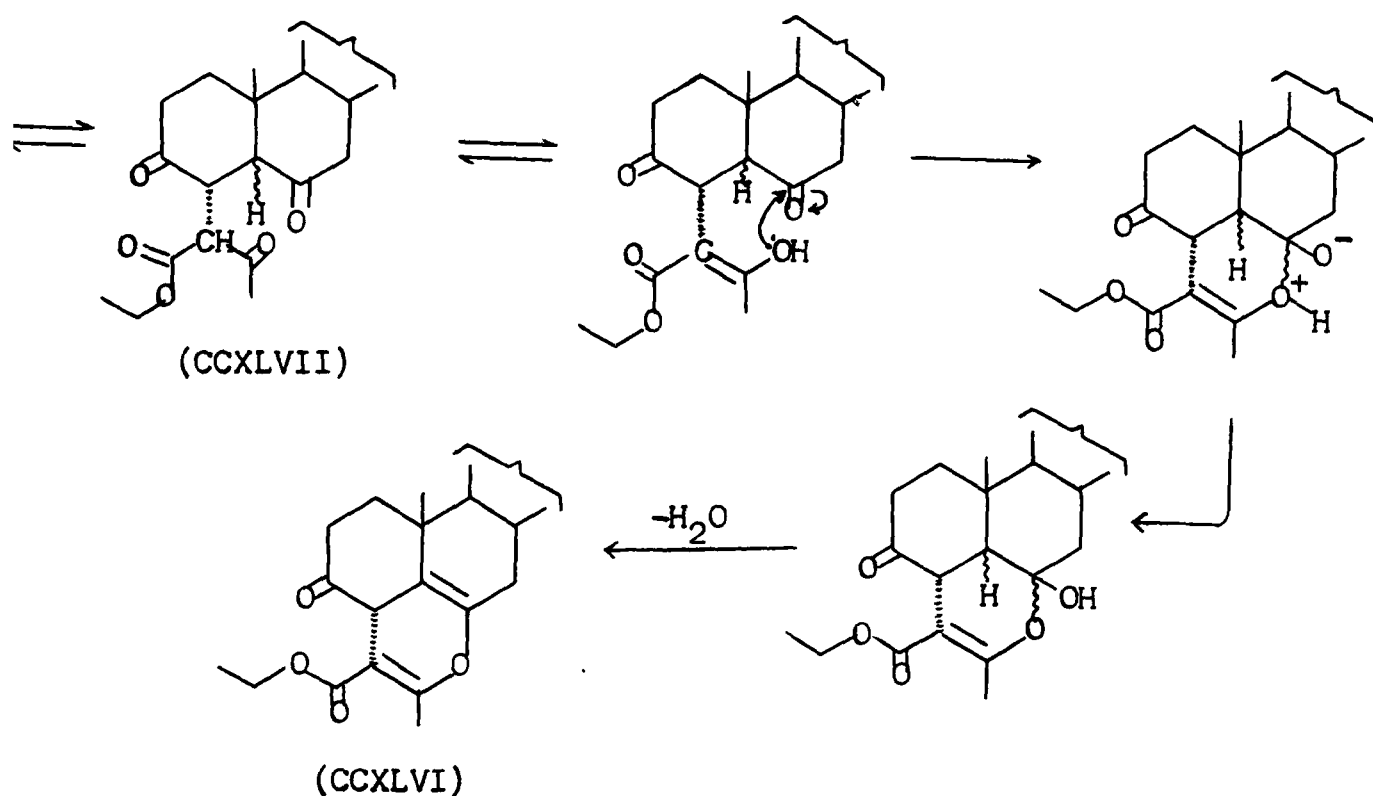
Theoretically two isomeric products are expected from the above reaction involving the ketone (CCXIV) and ethylacetoacetate and they have been formulated as (CCXLVI) and (CCXLVIa). The compound m.p. 147° analysed for $C_{33}H_{50}O_4$. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 510 ($C_{33}H_{50}O_4$). The i.r. spectrum of the compound gave relevant bands at 1720, 1710, 1645, 1585 and 1250 cm^{-1} . The bands at 1720 and 1710 cm^{-1} can be assigned to the carbonyl function of conjugated 3'-carboethoxy group^{69,70} and to the isolated cyclohexane carbonyl, respectively. Strong bands at 1645 and 1585 cm^{-1} are ascribable to C=C bond in pyran type derivatives¹²¹, and the band at 1250 cm^{-1} is also observed for C-O stretching of ester. The i.r. values supported both the structures (CCXLVI) and (CCXLVIa). The n.m.r. spectrum of the compound m.p. 147° gave a quartet at δ 4.25 ($J=7\text{ Hz}$) integrating for 2 protons which could be assigned to the methylene protons of the carboethoxy group ($\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$)⁶⁸; a broadened singlet at δ 2.75 integrating for one proton can be assigned to $\text{C}_4\text{-H}$ in (CCXLVI), which is also allylic in nature. A singlet at

δ 2.5 integrating for 3 protons can be assigned to 2'-methyl protons ($\text{CH}_3\text{-C=C-}$). Another broad signal at δ 2.2 integrating for two protons is ascribable to $\text{C}_2\text{-H}_2$. A triplet for 3 protons at δ 1.36 ($J=7$ Hz) is assigned to methyl protons of carboethoxy group ($\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$). Other methyl protons were observed at δ 1.2, 0.91, 0.83 and 0.73. The u.v. spectrum [λ_{max} 258 nm (ϵ 2944), 212 nm (ϵ 8064)] also supported the pyran structure. There is one vital structural difference between (CCXLVI) and (CCXLVIa). The latter possesses a vinylic proton at C_4 . However, there was no signal observed below δ 4.25 upto δ 10. This therefore supported the structure (CCXLVI). Further more it was not possible to construct the Dreiding model of the compound having structure (CCXLVIa) which violates Bredt's rule. This discarded the possibility of structure (CCXLVIa).

The formation of the compound (CCXLVI) from the ketone (CCXIV) can be shown according to the mechanism^{64,82} proposed in scheme-13.

Scheme - 13





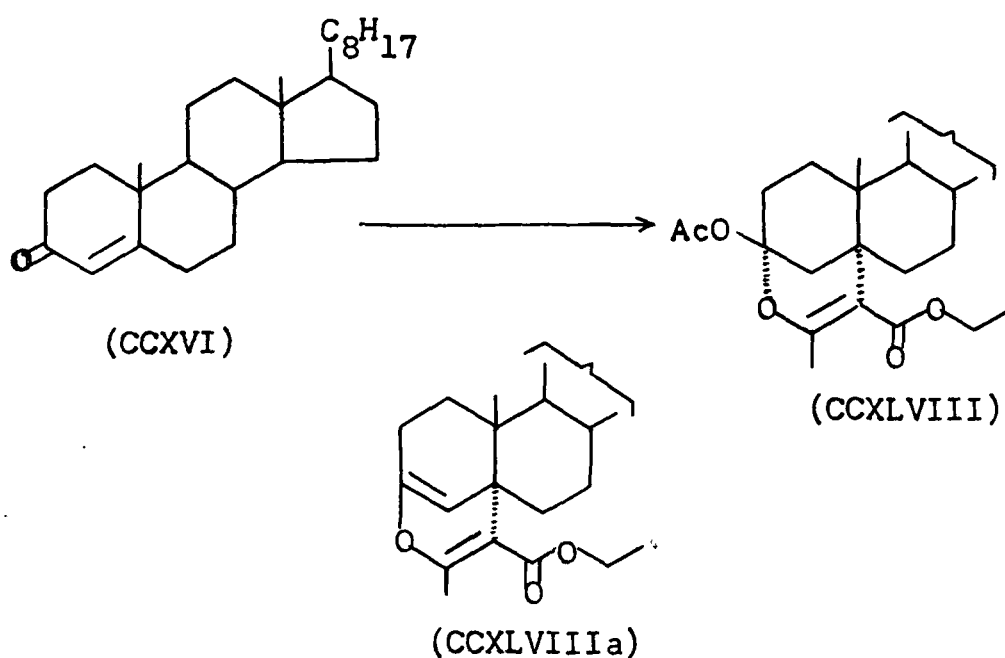
The first step is the conjugate addition (Michael) of the reagent at the α,β -unsaturated moiety to give the intermediate, 1,5-diketone (CCXLVII). The latter undergoes intramolecular cyclization followed by dehydration to give the compound (CCXLVI). The Dreiding model of the compound (CCXLVI) suggests, that the molecule is under lesser strain when pyran moiety is α -oriented.

Thus the compound m.p.147°, on the basis of elemental analysis, spectral properties and mechanistic considerations can best be characterized as 2'-methyl-3'-carboethoxy-3-oxo-5-cholesteno[4 α ,6-cd]- γ -pyran* (CCXLVI).

*The nomenclature used here is according to Green et al.⁸⁵

Reaction of 4-cholesten-3-one (CCXVI) with ethylacetoacetate

The ketone (CCXVI)¹¹⁷ on reaction with ethylacetoacetate, after usual workup and column chromatography gave a single compound, m.p.153°.

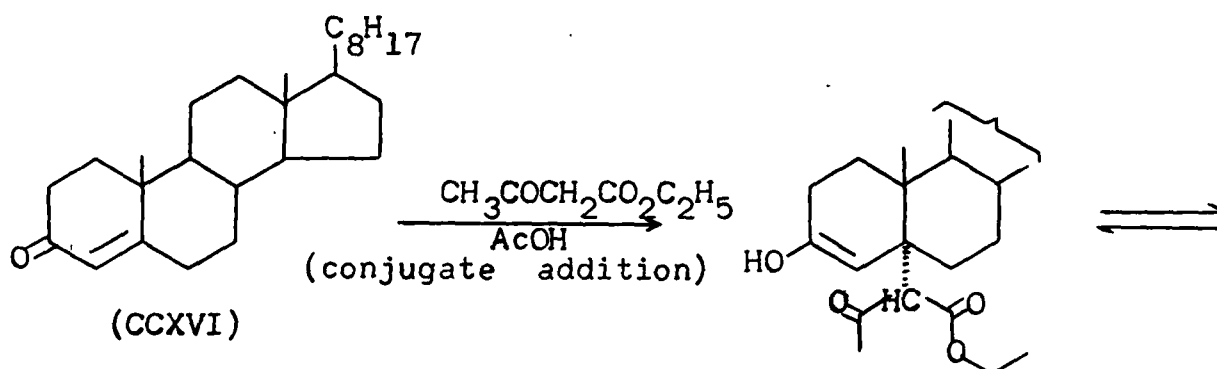


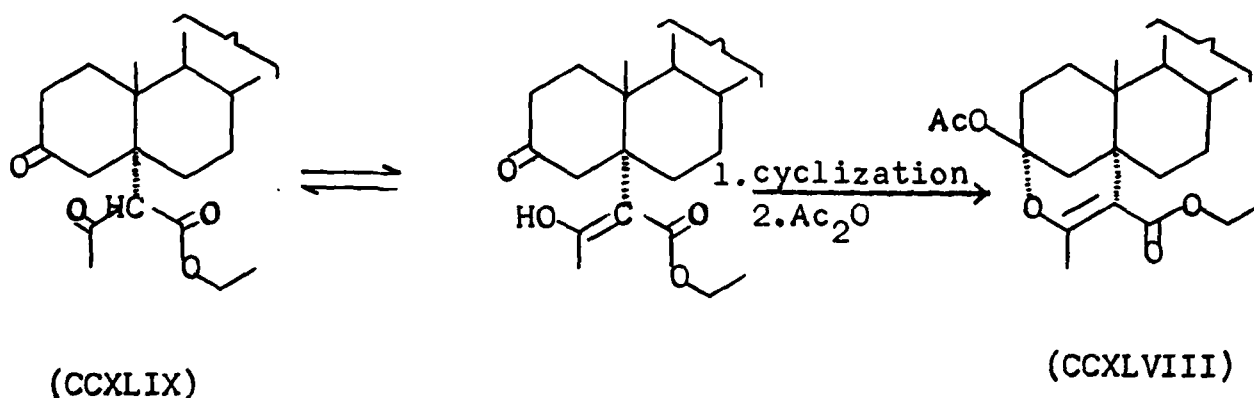
Theoretically it was expected to get the product (CCXLVIIIa) by the interaction of the ketone (CCXVI) and ethylacetoacetate. But the formation of the product (CCXLVIIIa) is not possible which is highly against Bredt's rule and also it was not possible to construct the Dreiding model of the compound (CCXLVIIIa). Hence the characterization of the compound m.p.153° was based upon the elemental analysis and spectral values.

The compound m.p.153° analysed for $C_{35}H_{56}O_5$. The i.r. spectrum of the compound gave bands at 1735 and 1720 cm^{-1} which may be assigned to the acetate carbonyl and to the conjugated carbonyl function of the carboethoxy group^{69,70}. Bands at 1630 and 1555 cm^{-1} may be assigned to the C=C bond in pyran type derivatives¹²¹. C-O stretching of ester was observed at 1260 cm^{-1} . The n.m.r. spectrum of the compound gave a quartet at δ 4.23 (J=7 Hz) integrating for two protons which was assigned to the methylene protons of the carboethoxy group ($CH_3-CH_2-O-C(=O)-$). Two singlets at δ 2.35 and 2.0 integrating for 3 protons each can be ascribed to the 2'-vinyl methyl ($CH_3-C=C-$)⁶⁸ and acetate methyl protons respectively. A triplet at δ 1.3 (J=7 Hz) can be ascribed to the methyl protons of carboethoxy group ($CH_3-CH_2-O-C(=O)-$). Signals for other methyl protons were observed at δ 1.1, 0.9, 0.8 and 0.7. Its u.v. spectrum gave absorption maxima at 257 nm and 211 nm. These spectral values supported the structure (CCXLVIII) for the compound m.p.153°.

The formation of the compound (CCXLVIII) may be shown according to the scheme-14^{68,82} as given below.

Scheme - 14





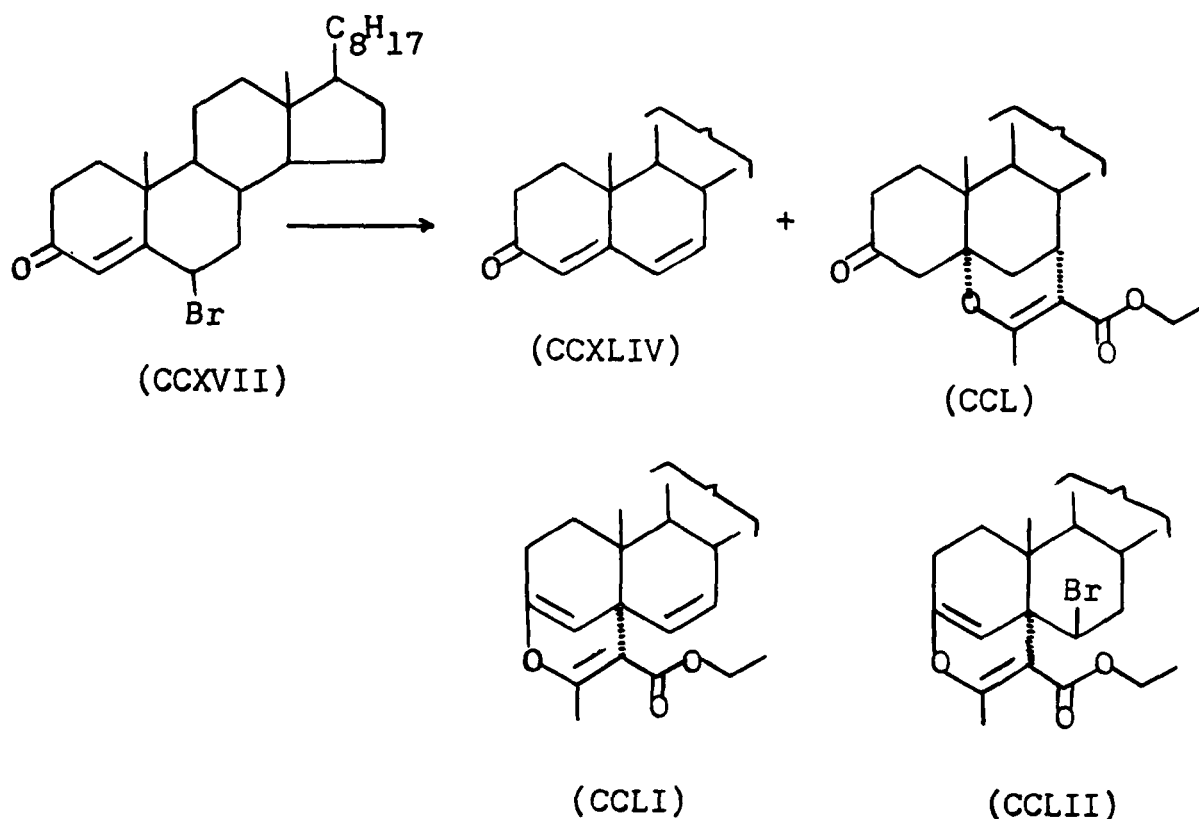
Reaction proceeds similarly as was proposed in scheme-13 except that the dehydration of the cyclized product does not take place which goes here against Bredt's rule. Instead it undergoes acetylation in presence of acetic anhydride to give the product (CCXLVIII).

Construction of the Dreiding model of the dihydropyran (CCXLVIII) reveals that with ring junction A/B trans the strain is slightly lesser than when the ring junction is cis. This appears to be in line with the general observation that the reagent prefers to approach steroidal molecules from the less crowded α -side.

Thus on the basis of elemental analysis, spectral values and mechanistic considerations the compound m.p. 153° can be characterized as 3 β -acetoxy-2'-methyl-3'-carboethoxy cholestan[3 α ,5 α -de]-dihydropyran (CCXLVIII).

Reaction of 6 β -bromo-4-cholesten-3-one (CCXVII) with ethylaceto-
acetate

The ketone (CCXVII)^{117a} on reaction with ethylaceto-
 acetate in the presence of zinc chloride, acetic acid and acetic
 anhydride afforded after usual work up and column chromatography
 two compounds m.p.79° and the other as a non-crystallizable oil.



The compound m.p.79° was identified as 4,6-cholestadien-
 3-one (CCXLIV) on the basis of its spectral data and by comparison
 with the authentic sample (m.p. and m.m.p.79°)^{117b}.

Characterization of the oil as 2'-methyl-3'-carboethoxy-3-oxocholestan[7 α ,5 α -de]-6,7-dihydropyran (CCL)

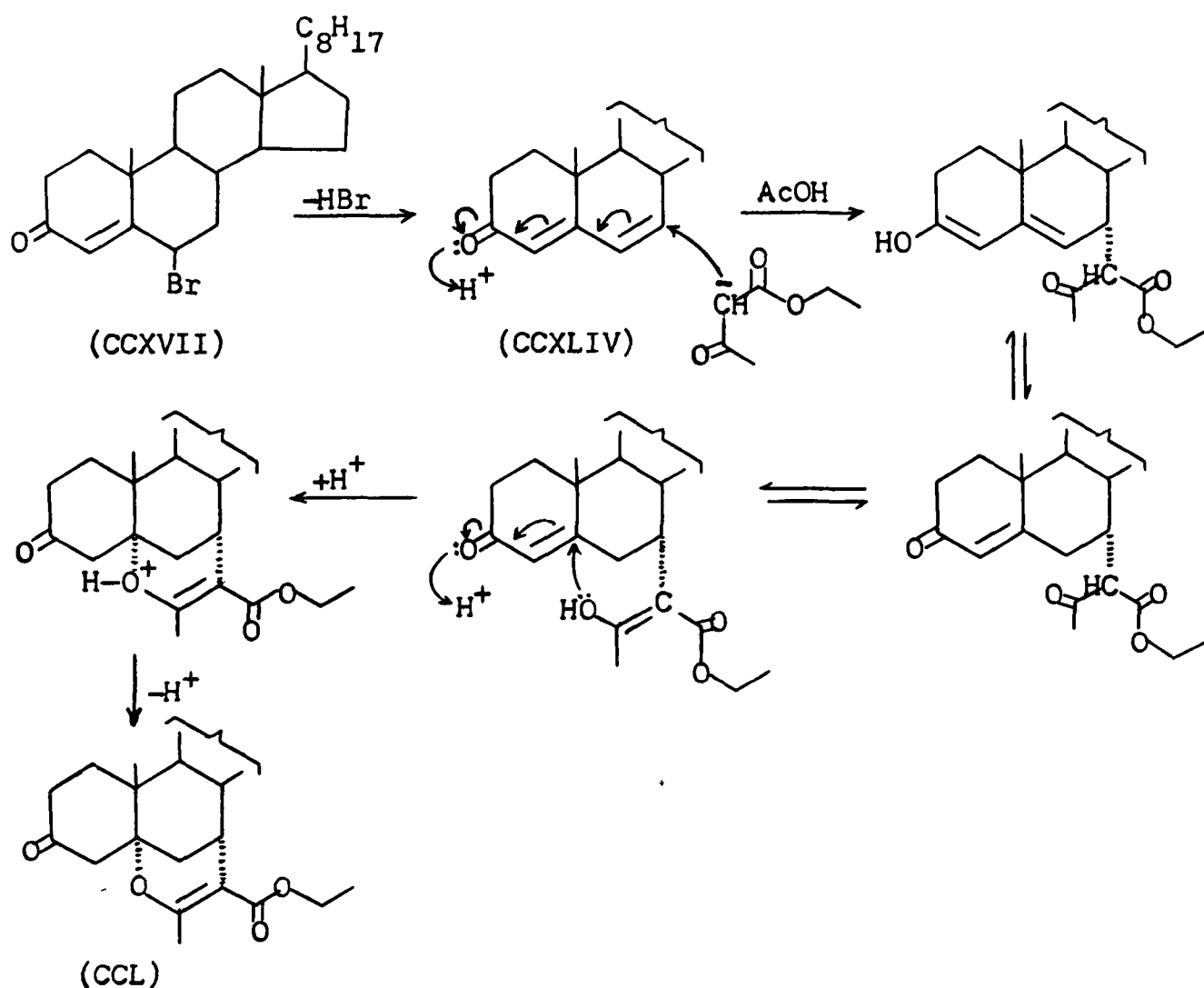
The oil obtained from the reaction of (CCXVII) with ethylacetoacetate gave negative Beilstein test and analysed for $C_{33}H_{52}O_4$. The theoretically possible bromine bearing compound (CCLII) can be discarded on the basis of Beilstein test and elemental analysis discarded the structure (CCLI) which has three oxygens only. Both the structures (CCLI) and (CCLII) can also be discarded, because their formation is against the Bredt's rule.

The i.r. spectrum of the compound gave strong bands at 1720 and 1705 cm^{-1} which may be assigned to the conjugated carbonyl function of the carboethoxy group^{69,70} and to the C_3 -ketone as in structure (CCL). Another band at 1580 cm^{-1} may be assigned to $C=C$ in pyrans¹²¹; C-O stretching of ester was recorded at 1260 cm^{-1} . N.m.r. spectrum gave a quartet at δ 4.20 ($J=7$ Hz) integrating for two protons, which was assigned to the methylene protons of the carboethoxy function ($CH_3-CH_2-O-\overset{O}{\parallel}C-$) and a singlet at δ 2.48 for 3 protons ascribable to vinyl methyl. A broad peak at δ 2.2 integrating for four protons was assigned to C_2-H_2 and C_4-H_2 and another broad peak at δ 2.0 for one proton was due to C_7 -allylic proton. A distorted triplet at δ 1.32 ($J=7$ Hz) integrating for three protons was assigned to the methyl protons of the carboethoxy group ($CH_3-CH_2-O-\overset{O}{\parallel}C-$); signals for other methyl protons were recorded

at δ 1.2, 0.9, 0.8 and 0.63. Its u.v. spectrum gave absorption maxima at 218 and 246 nm (ϵ 13312 and 6292).

On the basis of the elemental analysis and spectral values the oil may be characterized as 2'-methyl-3'-carboethoxy-3-oxocholestan[7 α ,5 α -de]-6,7-dihydropyran (CCL). Its formation may be proposed as shown in scheme-15.

Scheme - 15



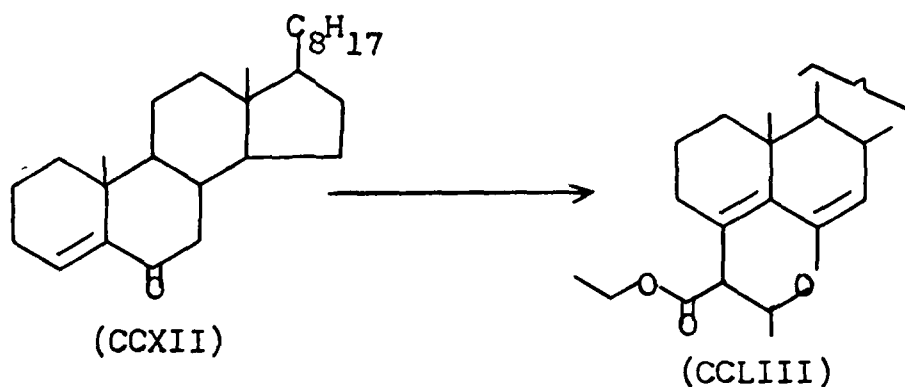
It is proposed that the bromoketone after the elimination of HBr gave the dienone (CCXLIV) and then the addition of the reagent takes place, which on intramolecular cyclization gave dihydropyran (CCL). The mechanism proposed in scheme-15 is supported by the observation that the dienone (CCXLIV) under similar conditions gave the compound (CCL).

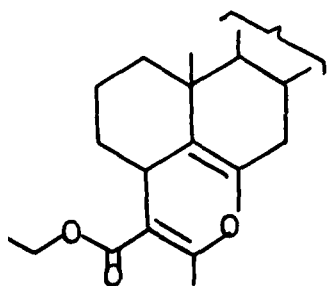
Reaction of 4,6-cholestadien-3-one (CCXLIV) with ethylacetoacetate

4,6-Cholestadien-3-one (CCXLIV)^{117b} on reaction with ethylacetoacetate afforded a single compound as noncrystallizable oil. The oil was found to be identical in all respects (t.l.c., i.r., n.m.r. and u.v.) with the compound (CCL) obtained from the reaction of the ketone (CCXVII) with ethylacetoacetate. This observation is in support of the mechanism (Scheme-15) proposed for the formation of (CCL) from the ketone (CCXVII).

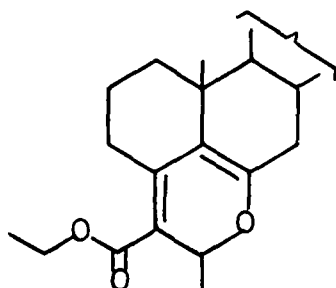
Reaction of 4-cholesten-6-one (CCXII) with ethylacetoacetate

The ketone (CCXII)¹⁰⁸ on treatment with ethylacetoacetate under similar conditions afforded after usual work up and column chromatography a single compound m.p.120°.

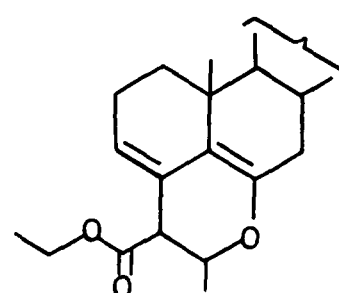




(CCLIV)



(CCLV)



(CCLVI)

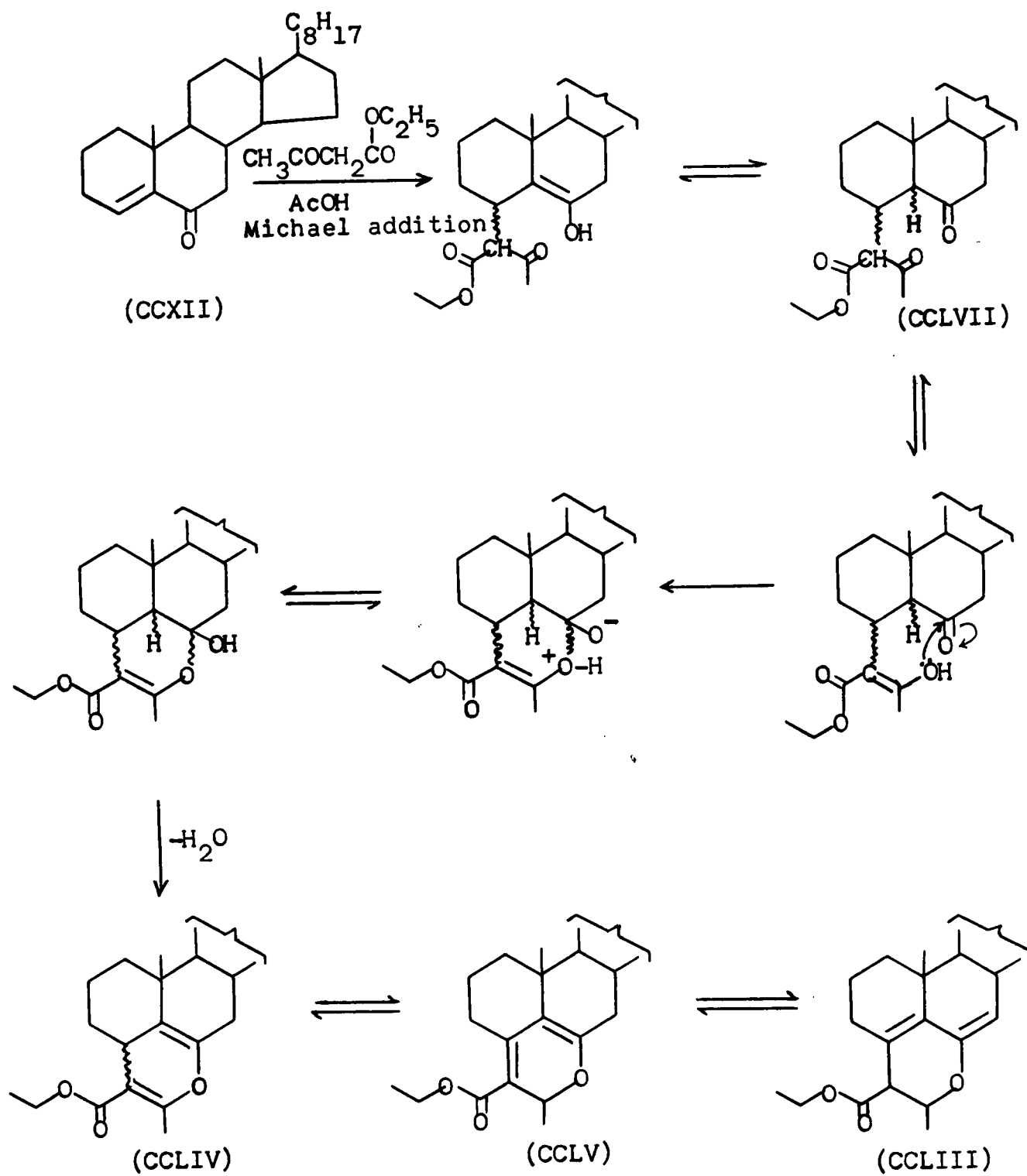
The compound m.p.120° analysed for C₃₃H₅₂O₃. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 496 (C₃₃H₅₂O₃). With this composition four isomeric structures (CCLIII-CCLVI) may be written for the compound m.p.120°. The i.r. spectrum of the compound gave a strong band at 1735 cm⁻¹ which may be assigned to the carbonyl function of the carboethoxy group; another strong band at 1650 cm⁻¹ may be assigned to C=C bond; C-O stretching of ester was observed at 1250 cm⁻¹. On the basis of the i.r. values the structures (CCLIV) and (CCLV) having conjugated carbonyl function can be discarded since the carbonyl frequency observed at 1735 cm⁻¹ shows the presence of an isolated carboethoxy carbonyl group. These values are compatible with both the structures (CCLIII) and (CCLVI). However, there is a differentiating feature between (CCLIII) and (CCLVI) and that is the environment of vinylic proton. In (CCLVI) the vinylic proton at C₃ is next to a methylene group whereas in (CCLIII) the vinylic proton at C₇ finds C₈ proton as the only immediate neighbouring proton. This difference has been fully realized. The n.m.r.

spectrum of the compound gave a singlet at δ 5.78 integrating for one proton which may be assigned to the C₇-vinylic proton as in structure (CCLIII). Dreiding model shows that the dihedral angle between C₇ and C₈ is of 90°. A quartet at δ 4.15 (J=7 Hz) integrating for three protons may be ascribed to the methylene protons of the carboethoxy group (CH₃-CH₂-O-C(=O)-) and methyne proton at C2'. A singlet at δ 3.2 integrating for one proton was assigned to the C3'- α -methyne proton. Allylic protons at C₃ and C₈ were recorded at δ 1.9. Methyl protons of carboethoxy group (CH₃-CH₂-O-C(=O)-) were recorded at δ 1.3 (J=7 Hz). Other methyl protons were observed at 1.2, 1.1, 0.9, 0.8 and 0.63. Its u.v. spectrum gave absorption maxima at 252 and 210 nm (ϵ 5818 and 4290).

These spectral values characterized the compound m.p. 120° as 2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydropyran (CCLIII).

Formation of the compound (CCLIII) from (CCXII) may be proposed as shown in scheme-16.

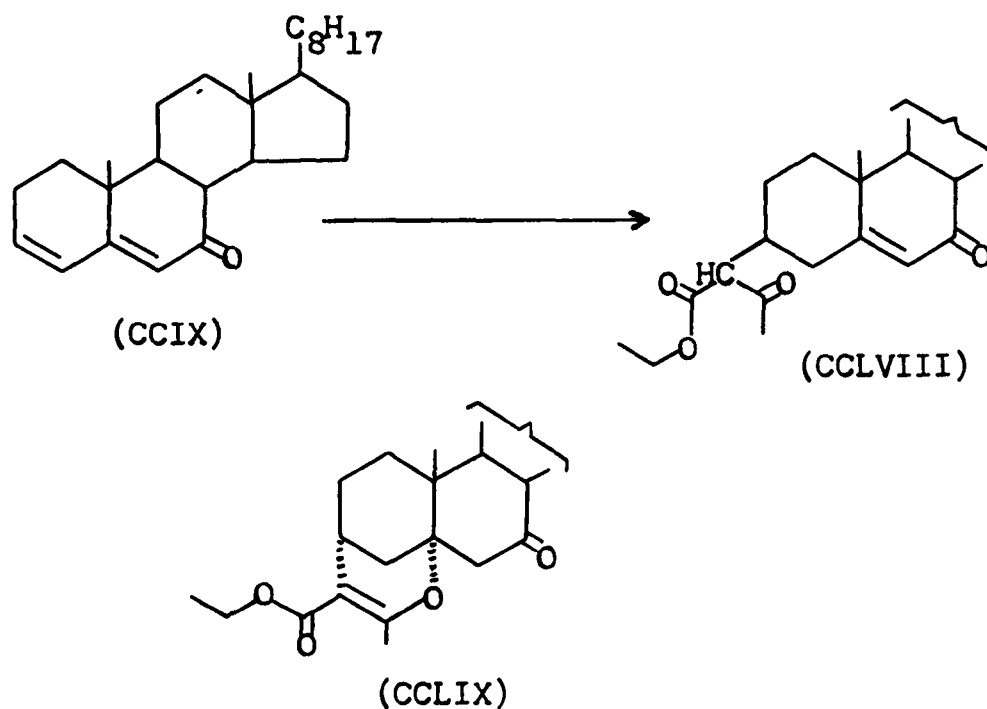
Scheme - 16



It is proposed that after the addition of the reagent, 1,5-diketone (CCLVII) on intramolecular cyclization followed by dehydration gave the pyran (CCLIV). Pyran (CCLIV) isomerises over to the pyran (CCLIII) in presence of acetic acid.

Reaction of 3,5-cholestadien-7-one (CCIX) with ethylacetoacetate

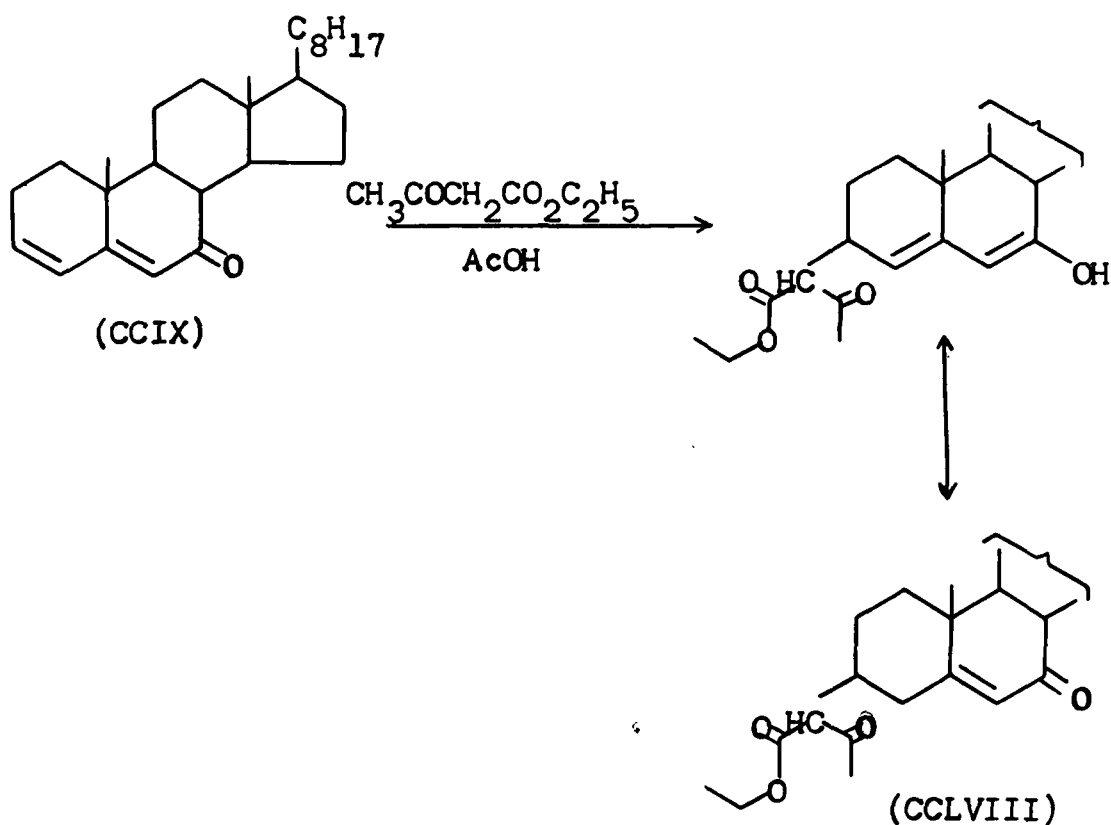
The dienone (CCIX)¹²² when subjected to the reaction of ethylacetoacetate afforded after usual work up and column chromatography a single compound as an oil.



The oil analysed for C₃₃H₅₂O₃. The i.r. spectrum showed bands at 1725 (CH₃-CH₂-O-C=O), 1710 (CH₃-C(=O)-CH-), 1670, 1620 (-C=C-C(=O)-)

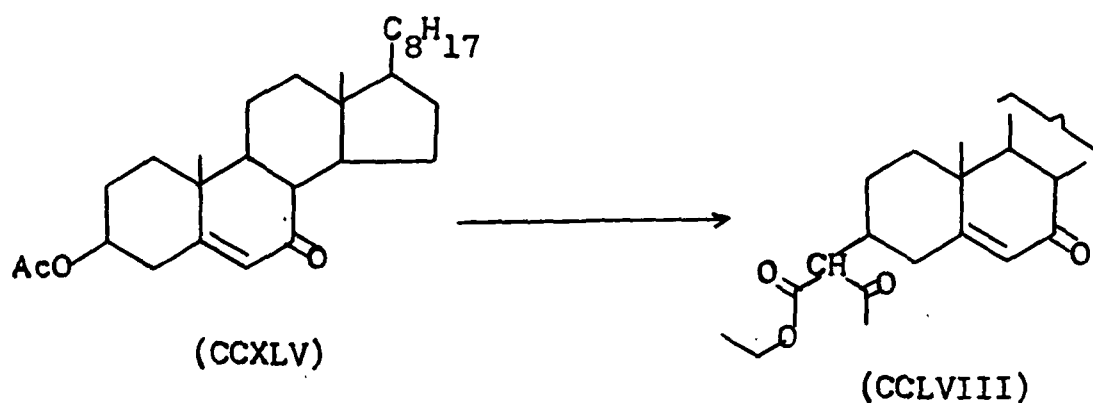
and 1250 cm^{-1} (C-O). The n.m.r. spectrum showed signals at δ 5.91 s (1H, C₆-vinylic), 4.25 q (J=7 Hz, carboethoxymethylene), 3.7 s (less than a proton, 1' α -methyne), 2.3 s (3H, CH₃CO), 1.2, 0.91, 0.83 and 0.7 (other methyl protons). The signal at δ 2.3 is at lower field than usually observed for CH₃-C(=O)-. λ_{max} 238 nm, Taking the spectral features into account the compound is better represented as (CCLVIII) rather than (CCLIX). Thus on the basis of elemental analysis and spectral data the oil may be characterized as 7-oxo-3 β -(1'-carboethoxypropan-2'-one)-5-cholestene. Its formation may be proposed as shown in scheme-17.

Scheme - 17



The mechanism further supported the views expressed earlier that conjugate (Michael) addition of the reagent takes place. However, the intermediate (CCLVIII) failed to cyclize to (CCLIX) under reaction conditions. This may in fact be explained by steric considerations though reaction at C_5 has been observed earlier.

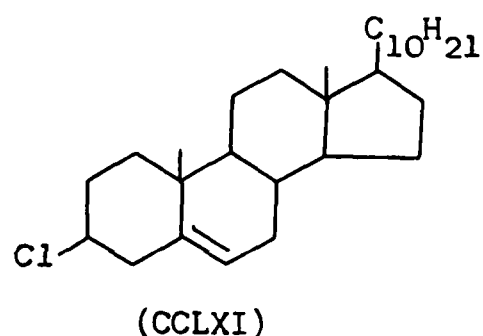
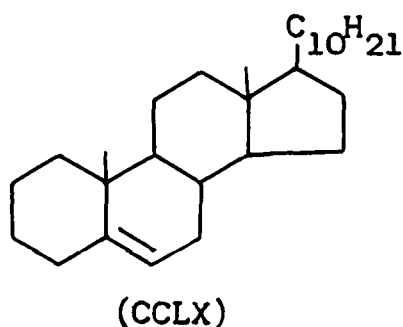
The reaction of 7-oxo-5-cholesten-3 β -yl acetate (CCXLV) with ethylacetoacetate under the similar reaction conditions afforded the same product (CCLVIII).

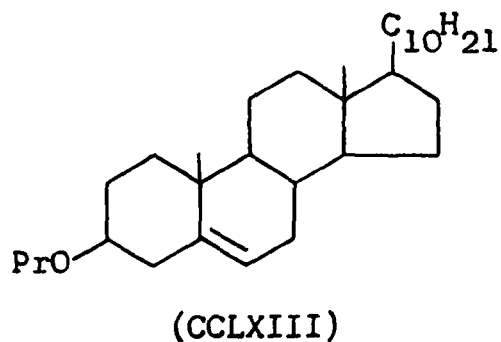
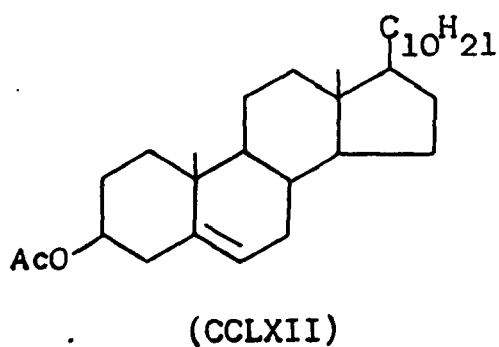


OXIDATION OF STEROIDAL OLEFINS WITH Mn(III) ACETATE

The oxidation of olefins with Mn(III) acetate, studied extensively, leads to the formation of γ -lactones alongwith other side products. Recently it has attracted the attention of chemists for the synthesis of a wide variety of compounds containing γ -lactone moiety. They are known to possess allergenic⁹⁰, growth inhibitor⁸⁹, antibacterial¹²³ and antitumor^{124,125} activity. Reaction of Mn(III) acetate with steroidal olefins has remained by large unexplored.

Recently the formation of the γ -lactone (CCLXI)¹⁰⁷ has been reported from the ketone (CCIX) by the reaction with Mn(III) acetate in the presence of acetic acid and acetic anhydride. General applicability of the reaction on steroidal olefins and nitroolefins in the cholestane series is in progress in our laboratory. This chapter deals with similar reactions on olefins in the stigmastane series. For the present study 5-stigmastene (CCLX), 5-stigmasten-3 β -yl chloride (CCLXI), 5-stigmasten-3 β -yl acetate (CCLXII) and 5-stigmasten-3 β -yl propionate (CCLXIII) have been selected.

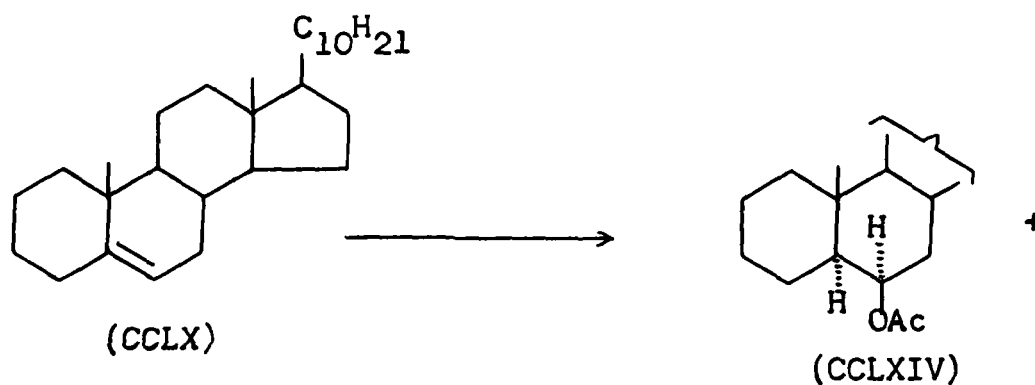


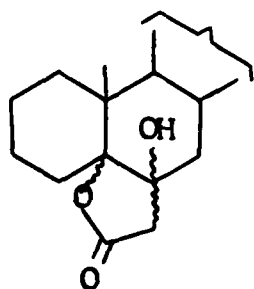


The γ -lactones and the other products obtained in the reaction have been characterized on the basis of elemental analysis and spectral values. A comparative study of the present findings and those obtained earlier¹²⁶ reveals interesting divergences/differences.

Reaction of 5-stigmastene (CCLX) with Mn(III) acetate in the presence of acetic acid and acetic anhydride

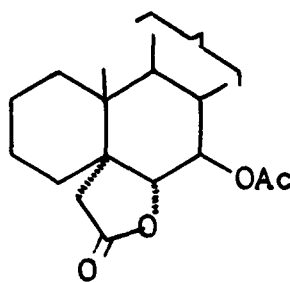
Reaction of 5-stigmastene (CCLX) with Mn(III) acetate, after usual workup and column chromatography afforded three compounds, oil (CCLXIV), solids m.p. 86° and m.p. 71° .





(CCLXV)

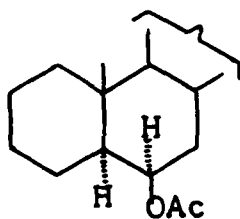
+



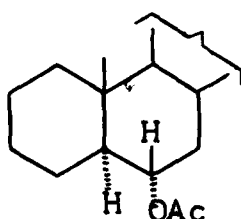
(CCLXVI)

Characterization of the oil as 5 α -stigmastan-6 β -yl acetate (CCLXIV)

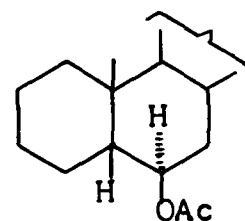
The oil analysed for $C_{31}H_{54}O_2$. The composition of the oil suggested the addition of acetic acid across the double bond. The i.r. spectrum of the compound gave important bands at 1735 and 1235 cm^{-1} for acetate function. With the consideration of the elemental analysis and i.r. values we may write six possible isomeric structures (CCLXIV and CCLXVII-CCLXIXb) for the oil.



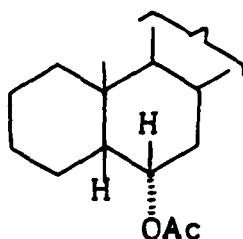
(CCLXIV)



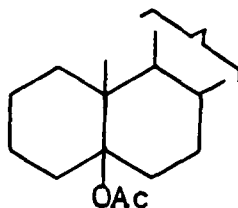
(CCLXVII)



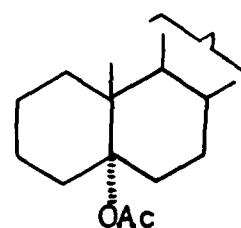
(CCLXVIII)



(CCLXIX)



(CCLXIXa)



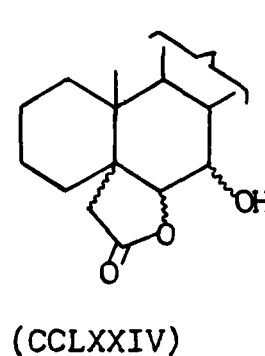
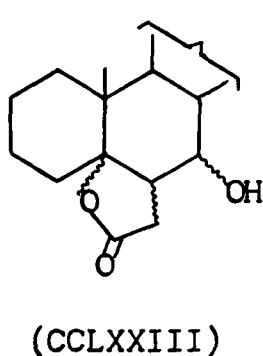
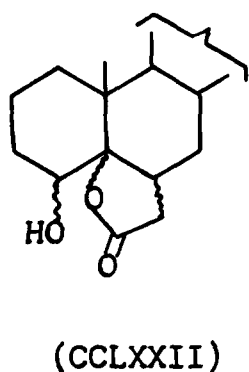
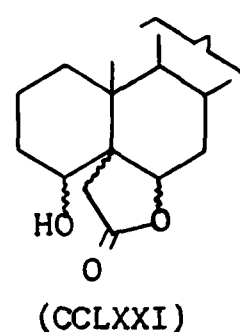
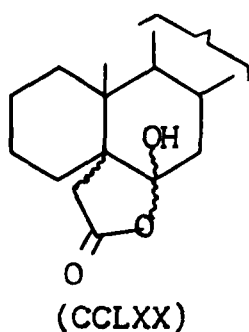
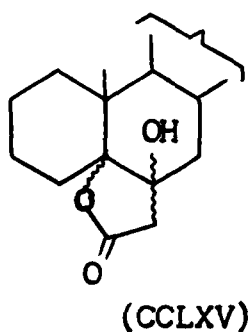
(CCLXIXb)

The n.m.r. spectrum of the oil gave a broad signal at δ 4.43 integrating for one proton which can be ascribed to a methyne proton having an acetate function. This ruled out the possibility of structures (CCLXIXa,b) which have tertiary acetate function. The final choice is based on the fact that the half band width of the signal at δ 4.43 is 4 Hz. This infact suggests that the C_6 -proton is equatorial (α -oriented) which can be satisfied by the structures (CCLXIV) and (CCLXVIII). In the isomeric structures (CCLXVII) and (CCLXIX) the same signal is expected to have large half band width as the C_6 -proton is axial (β -oriented). Other peaks were observed at δ 2.0s (acetate methyl), 1.2, 1.0, 0.9, 0.8 and 0.7 (other methyl protons). Out of the two structures (CCLXIV) and (CCLXVIII), structure (CCLXIV) is preferred because the trans A/B ring junction is of more common occurrence in steroids.

Thus the compound under discussion has been characterized as 5 α -stigmastan-6 β -yl acetate (CCLXIV).

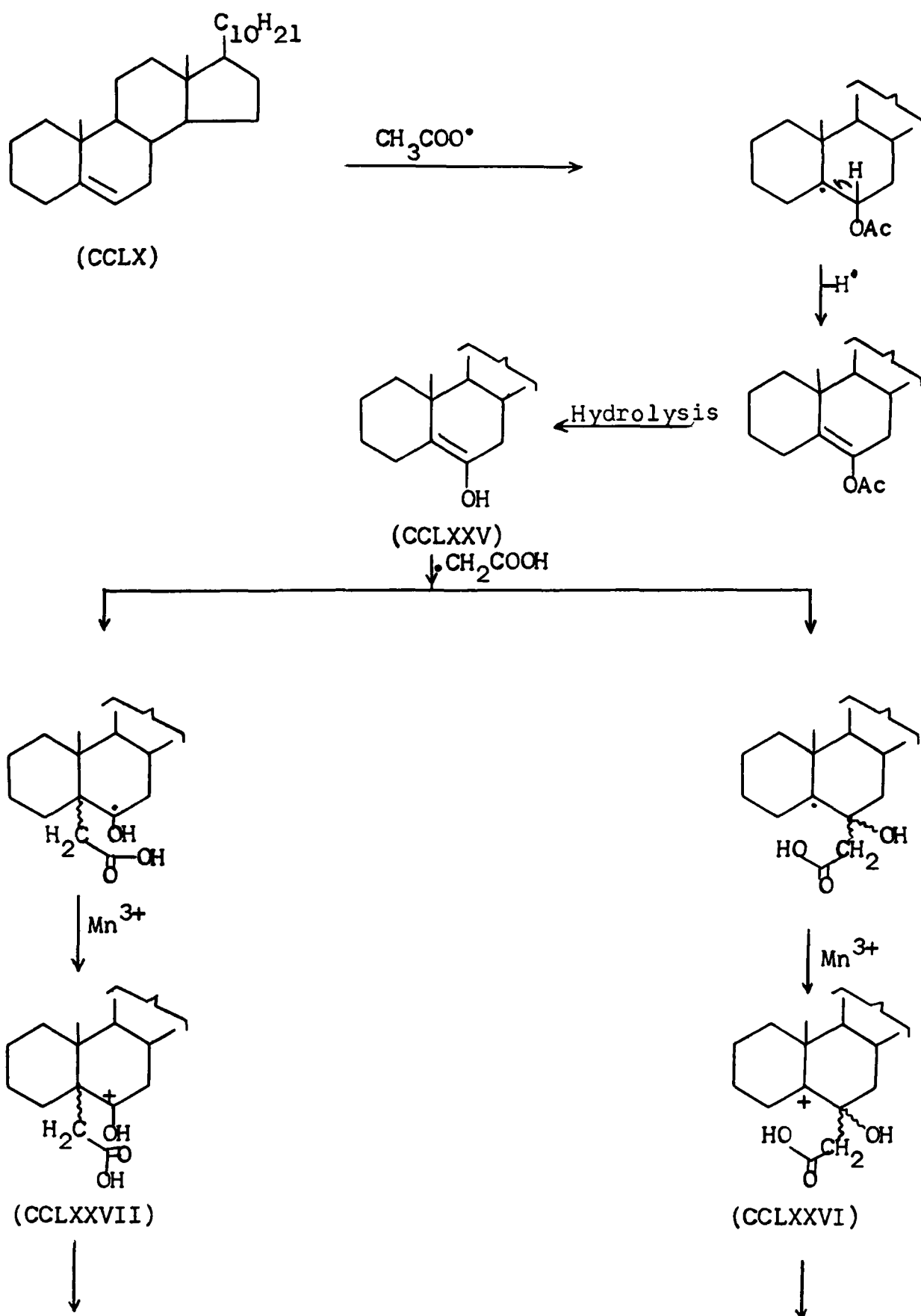
Characterization of the compound m.p. 86° as 5 ξ ,6 ξ -dihydroxy-stigmastan-6 ξ -yl acetic acid γ -lactone (CCLXV)

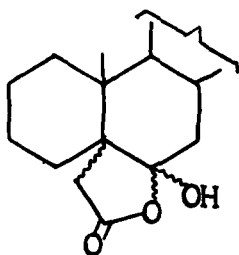
The compound m.p. 86° analysed for $C_{31}H_{52}O_3$ and its i.r. spectrum gave bands at 3400 (OH), 1770 and 1220 cm^{-1} (γ -lactone). On the basis of elemental analysis and i.r. values several possible structures, such as (CCLXV and CCLXX-CCLXXIV), can be written for the compound m.p. 86°.



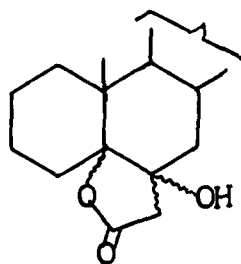
The n.m.r. spectrum of the compound was observed to be very simple in the sense that it showed only one significant peak as singlet at δ 2.33 alongwith other methyl signals at δ 1.2, 1.1, 0.97, 0.90, 0.8 and 0.7. The absence of downfield signals in the spectrum suggests that there is no proton on the carbon attached to an oxygen either of lactone or of hydroxy group. With this consideration the structures (CCLXXI-CCLXXIV) having secondary hydroxy group can be easily discarded. The spectral values go in favour of both the structures (CCLXV) and (CCLXX). The final choice is based upon the fact that the structure (CCLXV) is expected to be more stable as compared to the structure (CCLXX) since the latter is a hemiacetal type. Furthermore, the formation of both the compounds can be shown according to the scheme-18.

Scheme - 18





(CCLXX)



(CCLXV)

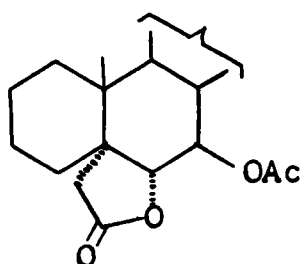
The mechanism involves the formation of carbonium ion intermediates (CCLXXVI) and (CCLXXVII) leading to (CCLXV) and (CCLXX), respectively. The intermediate carbonium ion (CCLXXVI) is expected to be more favoured due to its tertiary nature.

On the basis of the arguments advanced, the formulation of the compound m.p. 86° as 5 ξ , 6 ξ -dihydroxystigmastan-6 ξ -yl acetic acid γ -lactone (CCLXV) is preferred over its isomer (CCLXX). However, these spectral values could not help to decide about the stereochemistry of the groups in (CCLXV). Dreiding model suggests that the α -oriented lactone moiety is to be preferred.

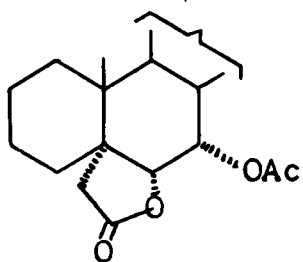
Characterization of the compound m.p. 71° as 7 β -acetoxy-6 α -hydroxy-stigmastan-5 α -yl acetic acid γ -lactone (CCLXVI)

The compound m.p. 71° analysed for $C_{33}H_{53}O_4$ showing the presence of four oxygen atoms in the molecule. The i.r. spectrum showed bands at 1780, 1735 and 1230 cm^{-1} indicating the presence of a γ -lactone ring and an acetate function which also accounts

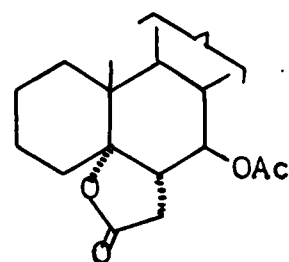
for the four oxygen atoms. On the basis of the elemental analysis and i.r. values several possible structures such as (CCLXVI and (CCLXVIa-g) can be written for the compound m.p.71°.



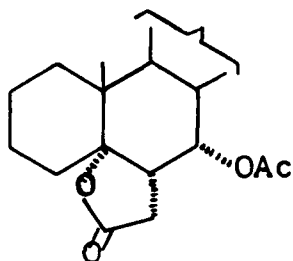
(CCLXVI)



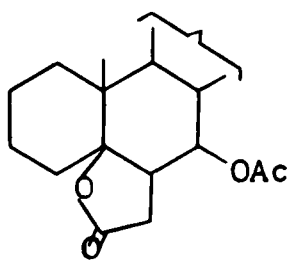
(CCLXVIa)



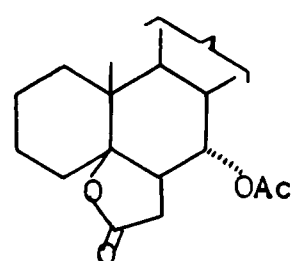
(CCLXVIb)



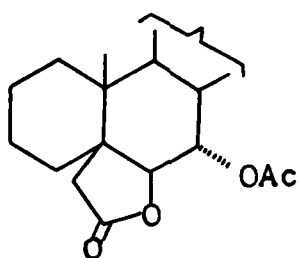
(CCLXVIc)



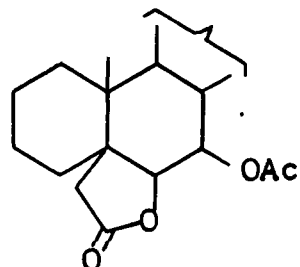
(CCLXVI d)



(CCLXVIe)



(CCLXVI f)

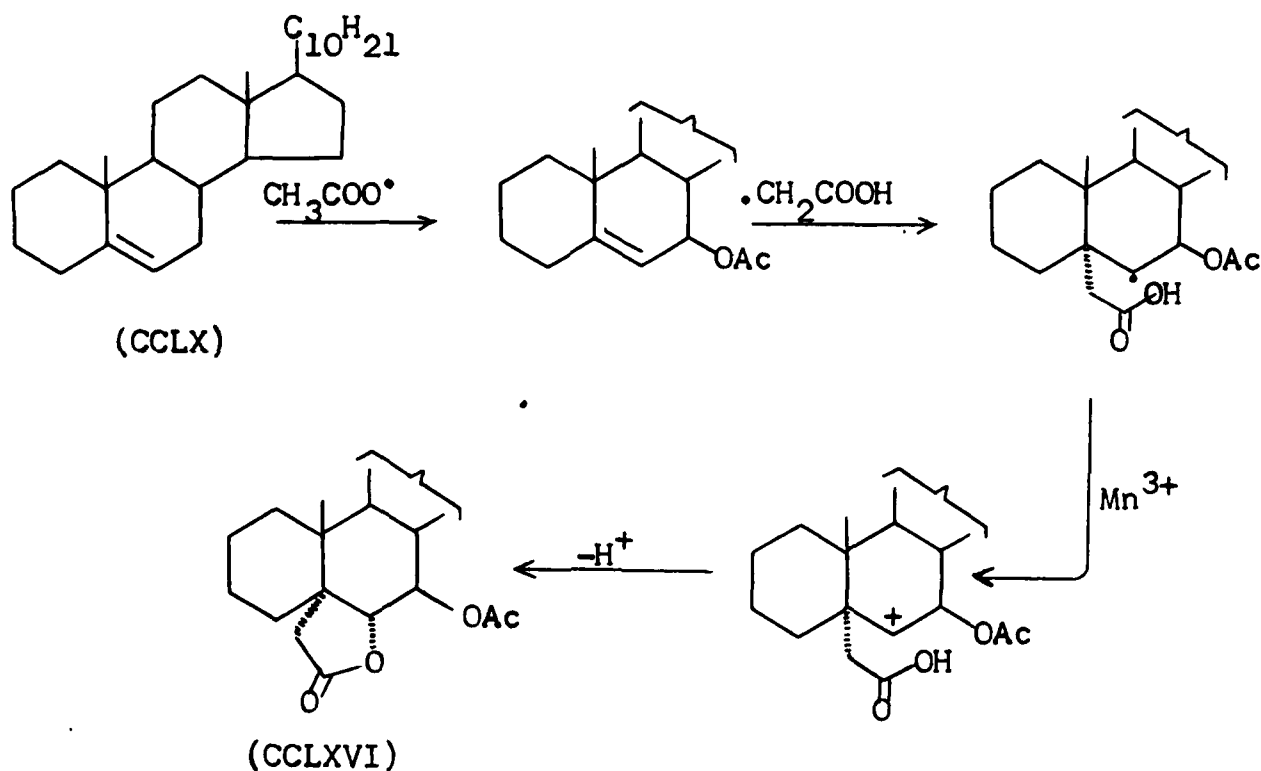


(CCLXVIg)

The n.m.r. spectrum gave signals at δ 5.7, 5.2, 2.4, 2.0, 1.1, 0.9, 0.8 and 0.7. The two signals at δ 5.7 doublet and 5.2 doublet of a doublet need special comments. At the first look the signal at δ 5.7 gave an impression that it may be a vinylic proton but the i.r. spectrum was devoid of any such band. The signals at δ 5.7d and 5.2dd combined together integrating for two protons only, indicate that there are two protons surrounded by electron-withdrawing groups, which are to be γ -lactone and acetate in this case. The signal at δ 5.7 as doublet integrating for one proton was assigned to the C_6 - β H (axial) and the signal at δ 5.2 as doublet of a doublet integrating for one proton was assigned to C_7 - α H (axial). It is pertinent to mention here that extra downfield shift of the two signals may be attributed to the fact that the two electro-negative groups are present at adjacent (C_6 - C_7) carbon atoms. The signals at δ 2.4 and 2.0 as singlets were assigned to the methylene protons of γ -lactone moiety, and acetate methyl protons respectively. Other methyl protons were assigned values δ 1.1, 0.9, 0.8 and 0.7. In the light of these considerations the most preferred structure is (CCLXVI), and therefore, its isomeric structures, such as (CCLXVIa-g) are ignored.

The formation of the compound (CCLXVI) from the alkene (CCLX) can be explained as shown in scheme-19^{94,99,100}.

Scheme - 19

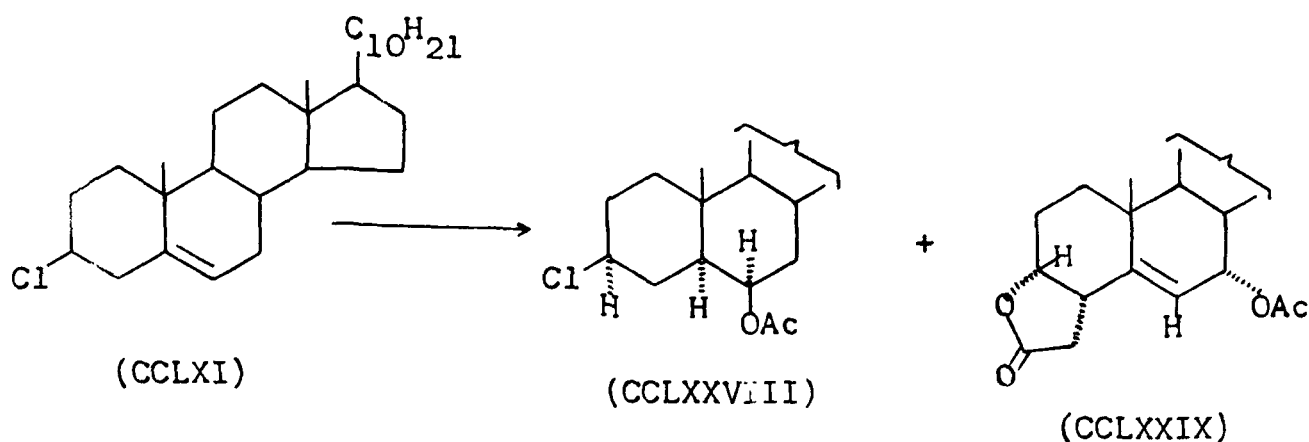


In this scheme it is proposed that the first step is the allylic acetylation, which is preferably in the same ring and then the attack of carboxymethyl radical on the olefin followed by oxidation and cyclization gave (CCLXVI).

Hence on the basis of foregoing discussion the compound m.p. 71° may be characterized as 7β -acetoxy- 6α -hydroxystigmastan- 5α -yl acetic acid γ -lactone (CCLXVI).

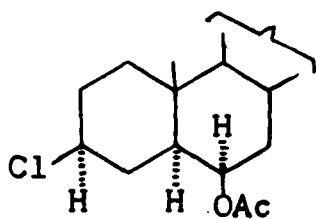
Reaction of 5-stigmasten-3 β -yl chloride (CCLXI) with Mn(III) acetate

5-Stigmasten-3 β -yl chloride (CCLXI) on similar reaction with Mn(III) acetate afforded after usual workup and column chromatography two non-crystallizable viscous oily products (CCLXXVIII) and (CCLXXIX), referred to as O₁ and O₂ respectively.

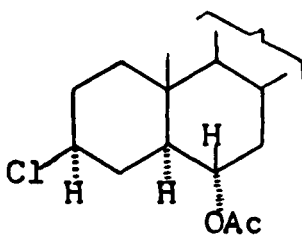


Characterization of O₁ as 3 β -chloro-5 α -stigmastan-6 β -yl acetate (CCLXXVIII)

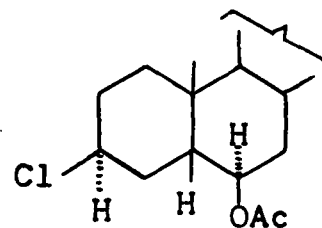
The oily product O₁ analysed for C₃₁H₅₃O₂Cl. It gave positive Beilstein test. The composition suggests that acetic acid has been added across the double bond during the reaction. The various structures which may be written for the composition (C₃₁H₅₃O₂Cl) are (CCLXXVIII and CCLXXX-CCLXXXII).



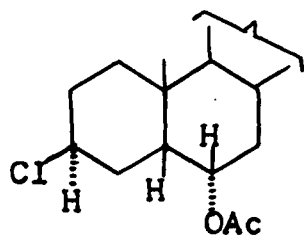
(CCLXXVIII)



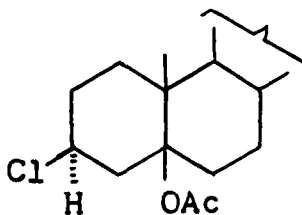
(CCLXXX)



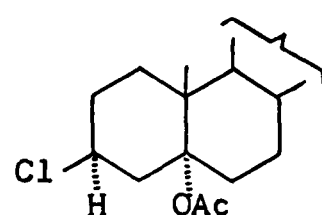
(CCLXXXa)



(CCLXXXb)



(CCLXXXI)



(CCLXXXII)

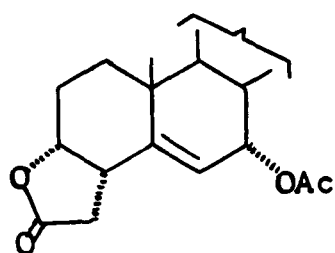
The i.r. spectrum of the oil O_1 gave bands at 1735, 1235 (acetate) and 760 cm^{-1} (C-Cl). The n.m.r. spectrum of O_1 gave a singlet with slight shoulder at δ 4.46 having half band width 4 Hz, integrating for one proton, which can be assigned to the C_6 -proton as in structure (CCLXXVIII) or (CCLXXX and CCLXXXa,b). This discarded the possibility of structures (CCLXXXI) and (CCLXXXII). Now the choice is narrowed down to the structures (CCLXXVIII and CCLXXXa,b). The splitting of C_6 -proton (half band width 4 Hz) suggested that the C_6 -proton is equatorial (α -oriented). This discarded the possibilities of structures (CCLXXX and CCLXXXb), where the C_6 -proton is axial. Another broad peak at δ 3.66 with half band width 16 Hz and integrating for one proton was assigned

to the $C_3-\alpha H$. The ring junction A/B (trans) was evident from the half band width of $C_3-\underline{H}$ signal. Therefore implying the C_3-H is α and axial, the ring junction A/B is trans¹²⁷. Methyl signals were observed at δ 2.0s (3H, CH_3COO), 1.2, 1.06, 0.9, 0.8 and 0.7. The O_1 was thus identified as 3 β -chloro-5 α -stigmastan-6 β -yl acetate (CCLXXVIII).

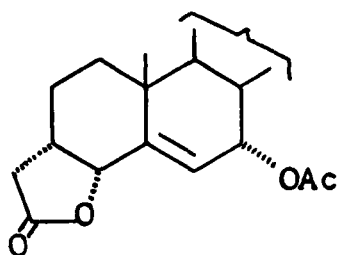
Characterization of O_2 as 7 α -acetoxy-3 α -hydroxystigmast-5-en-4 α -yl acetic acid γ -lactone (CCLXXIX)

The oil O_2 gave negative Beilstein test and analysed for $C_{33}H_{52}O_4$. The composition is substantiated by the highest mass peak at m/z 452 which can be explained to be obtained from the molecular ion by ready loss of acetic acid (HOAc). This suggests that chlorine atom has been removed and two moieties CH_2COO and CH_3COO have been incorporated during the reaction. The i.r. spectrum of the oil O_2 gave bands at 1770, 1735 and 1230 cm^{-1} (γ -lactone and acetate function); another band at 1640 cm^{-1} suggests the presence of a $C=C$.

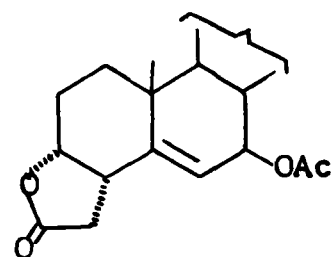
In accordance with the elemental composition and i.r. values observed for the oil O_2 several isomeric structures such as (CCLXXIX and CCLXXXIII-CCLXXXIX) may be written.



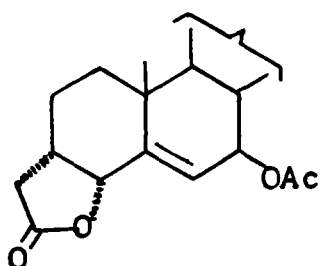
(CCLXXIX)



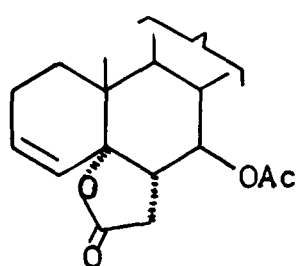
(CCLXXXIII)



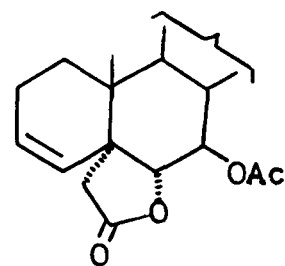
(CCLXXXIV)



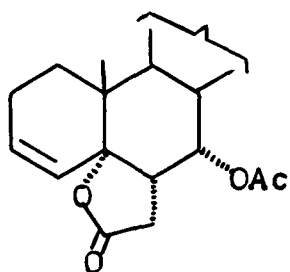
(CCLXXXV)



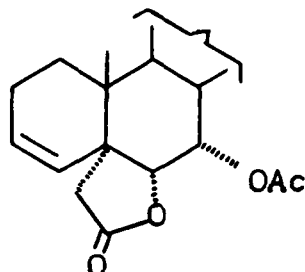
(CCLXXXVI)



(CCLXXXVII)



(CCLXXXVIII)

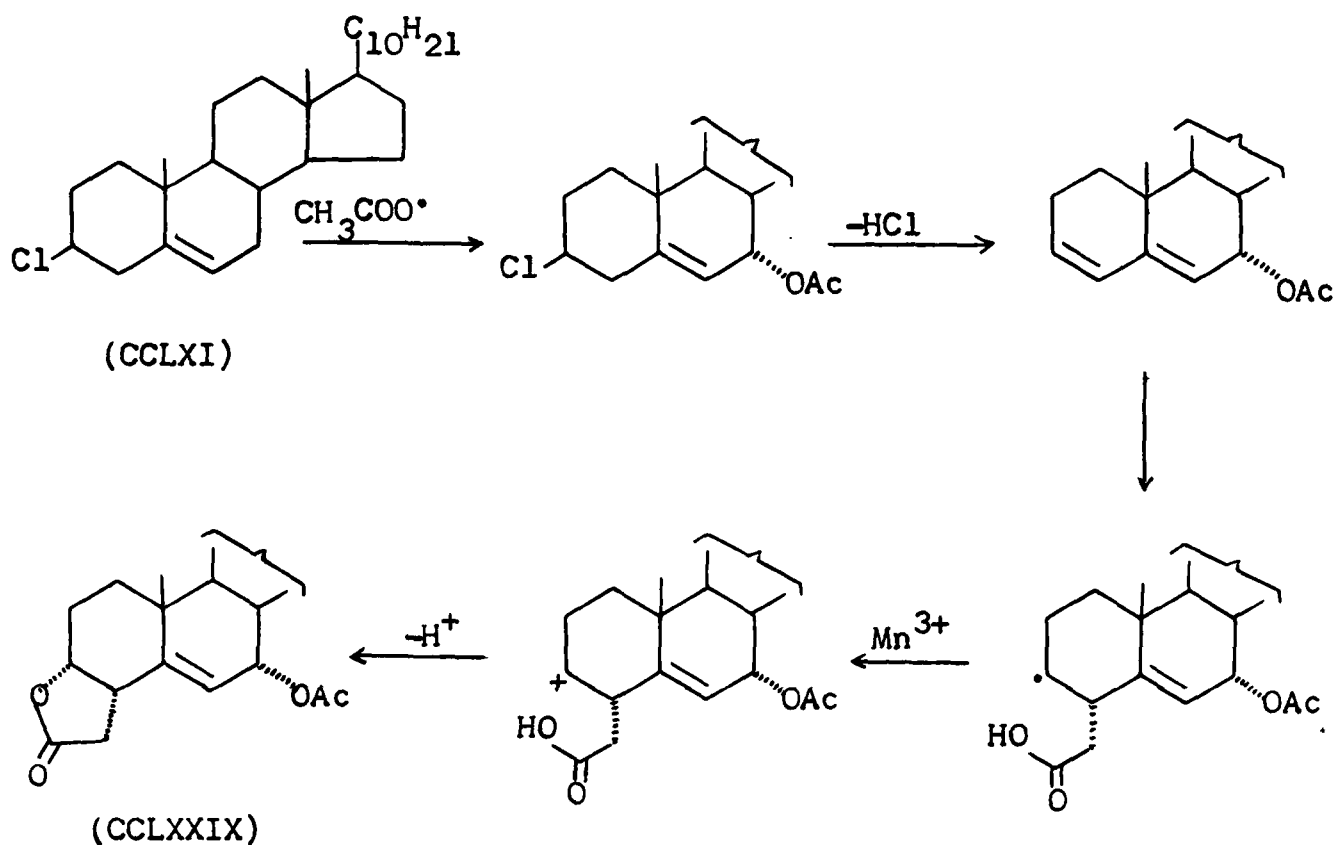


(CCLXXXIX)

The n.m.r. spectrum of the oil O_2 gave a doublet at δ 6.05 ($J=9$ Hz) integrating for one proton, which may be assigned to the C_6 -vinylic proton as in structures (CCLXXIX and CCLXXXIII-CCLXXXV). The structures (CCLXXXVI-CCLXXXIX) were discarded, which have two vinylic protons. Another doublet at δ 5.33 ($J=9$ Hz) integrating for one proton may be assigned to the C_7 - βH (pseudo equatorial). This suggests that the acetate at C_7 is α oriented (pseudo axial). The downfield shift of the signal is due to the

proton being allylic in nature. The structures (CCLXXXIV) and (CCLXXXV) were discarded which have $C_7-\alpha H$ (pseudo axial). In n.m.r. spectrum another broad signal at δ 4.43 with half band width 5 Hz for one proton was assigned to the $C_3-\beta H$ ¹²⁶ as in structure (CCLXXIX). Splitting of the $C_3-\beta H$ ($W_{1/2}=5$ Hz) suggested that the proton is pseudo equatorial (β -oriented) and thus the lactone moiety at C_3 and C_4 is α -oriented. A broad singlet at δ 2.4 integrating for two protons was assigned to the methylene protons of the γ -lactone moiety. Methyl protons were recorded at δ 2.0 (acetate), 1.1, 1.03, 0.9, 0.8 and 0.7. These spectral values suggested structure (CCLXXIX) for the oil O_2 . The formation of the compound (CCLXXIX) may be proposed as shown in scheme-20^{94,99,100}.

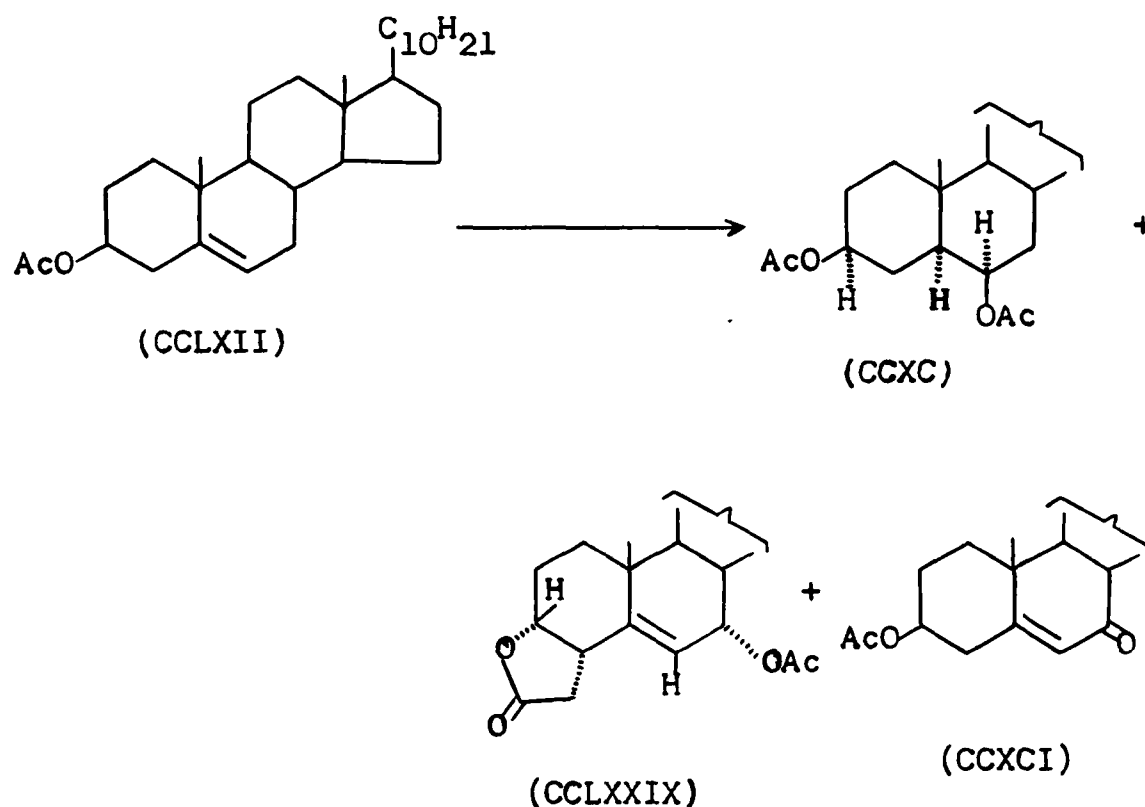
Scheme - 20



Thus the compound, O_2 can best be identified as 7α -acetoxy- 3α -hydroxystigmast-5-en- 4α -yl acetic acid γ -lactone (CCLXXIX).

Reaction of 5-stigmasten- 3β -yl acetate (CCLXII) with Mn(III) acetate

Reaction of the olefin (CCLXII) with Mn(III) acetate under similar conditions gave three compounds, two as oily products (CCXC) and (CCLXXIX) referred to as O_3 and O_4 respectively and third was a solid m.p.168-169°.



Characterization of O_3 as 5 α -stigmastan-3 β ,6 β -yl diacetate (CCXC)

The oil O_3 analysed for $C_{33}H_{56}O_4$. The composition suggested the addition of acetic acid across the double bond. The i.r. spectrum gave a very strong band at 1735 cm^{-1} which indicated the presence of two acetate carbonyls and no absorption for $C=C$ was observed. Strong bands at 1230 and 1035 cm^{-1} supported the presence of acetate functions. The n.m.r. spectrum gave a broad peak merged with a sharp peak at $\delta\ 4.5$ integrating for two protons. It can be ascribed to the signals due to C_3 - αH axial proton (broad) and C_6 - αH equatorial proton (tall). A singlet at $\delta\ 2.05$ integrating for six protons was assigned to the protons of two acetate methyls. Other methyl protons were recorded at $\delta\ 1.1, 1.01, 0.88, 0.7$ and 0.6 . These spectral values supported the structure (CCXC) for the oil referred to as O_3 .

Characterization of O_4 as 7 α -acetoxy-3 α -hydroxystigmast-5-en-4 α -yl acetic acid γ -lactone (CCLXXIX)

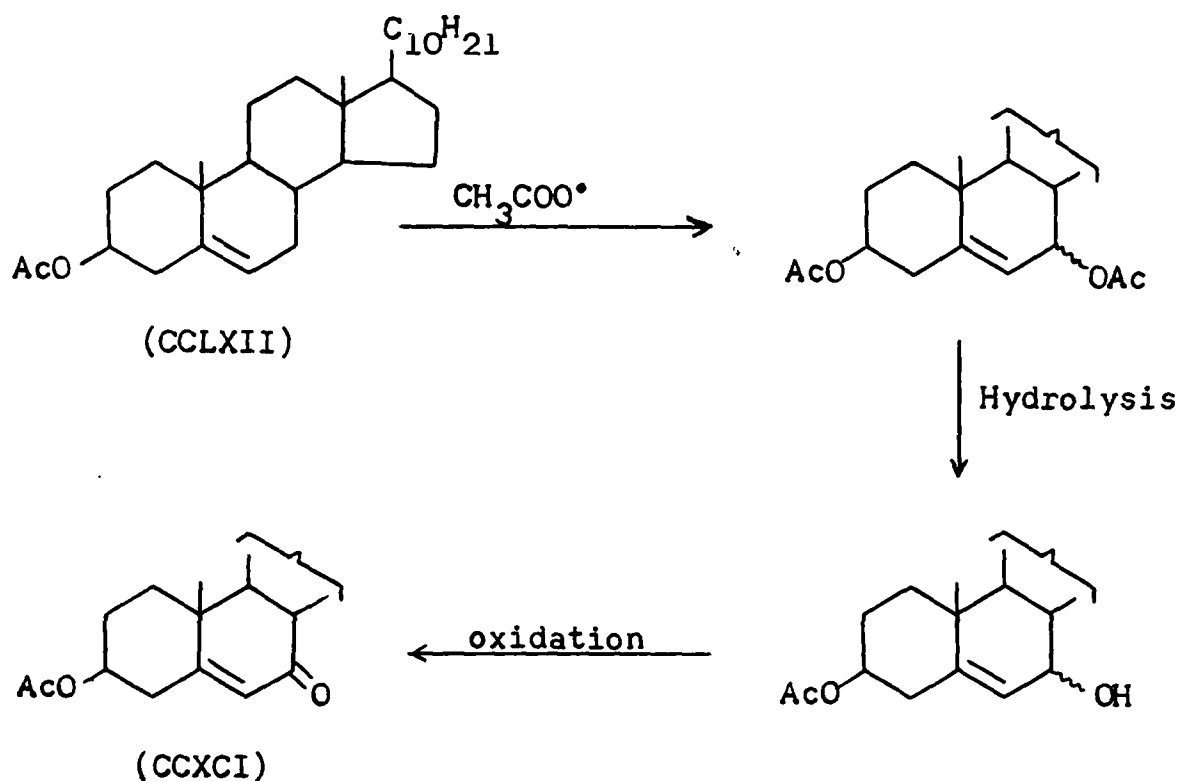
The oil, O_4 was found to be similar in all respects (t.l.c., i.r. and n.m.r.) with the oil O_2 obtained earlier.

Characterization of the compound m.p.168° as 7-oxo-5-stigmasten-3β-yl acetate (CCXCI)

The compound m.p.168° was found to be similar in all respects (m.p., m.m.p.¹²⁸, t.l.c., i.r. and n.m.r.) with 7-oxo-5-stigmasten-3β-yl acetate (CCXCI).

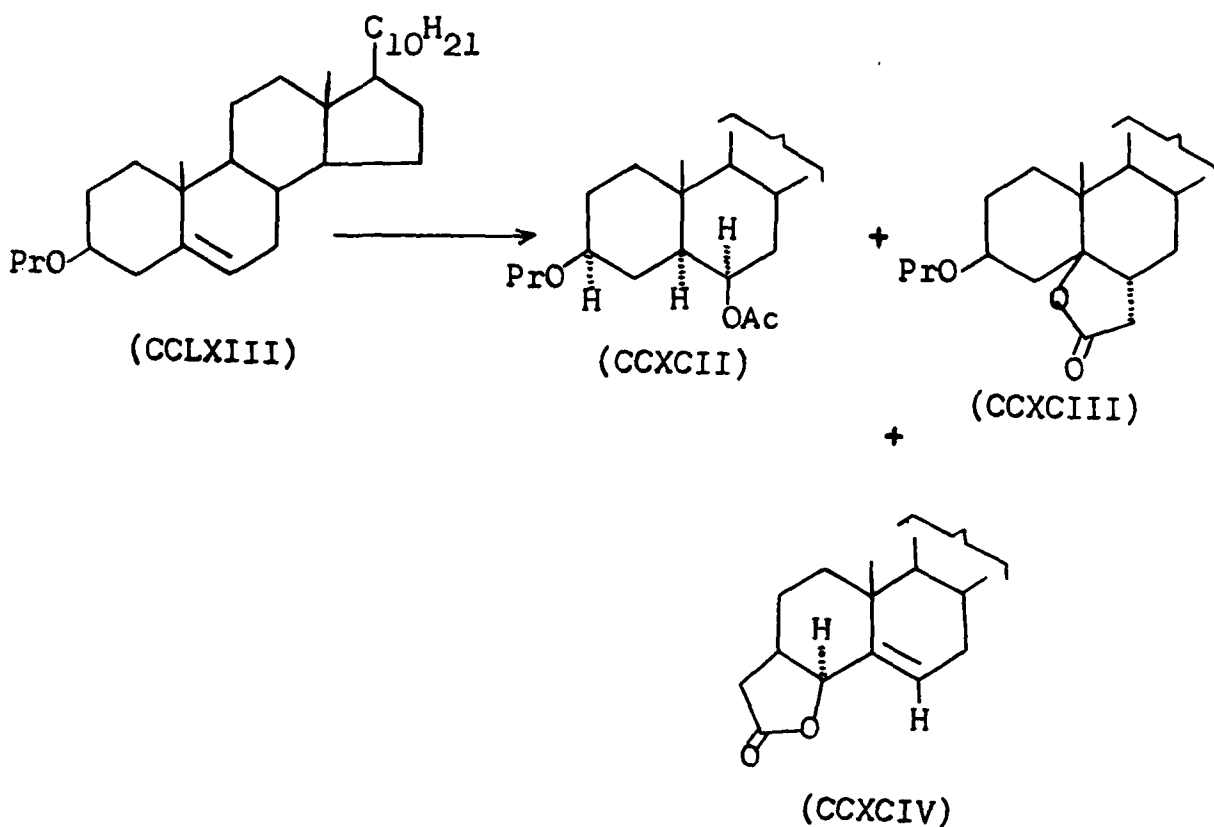
The formation of the compound (CCXCI) from the olefin (CCLXII) may be proposed as shown in scheme-21.

Scheme - 21



Reaction of 5-stigmasten-3 β -yl propionate (CCLXIII) with Mn(III) acetate

5-Stigmasten-3 β -yl propionate (CCLXIII) on reaction with Mn(III) acetate under similar conditions afforded after usual workup and column chromatography, three compounds. The first one was a non-crystallizable oily material O₅; other two were found to be solids m.p.176° and 95°.



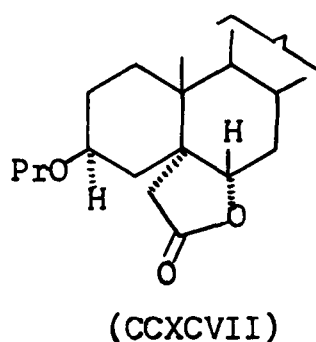
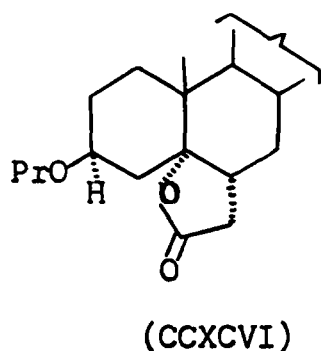
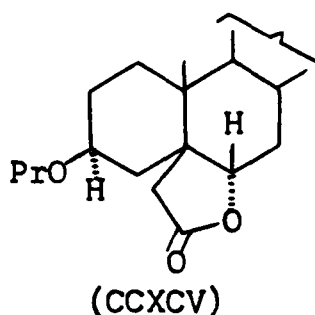
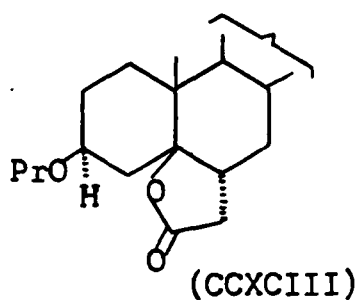
Characterization of O_5 as 6 β -acetoxy-5 α -stigmastan-3 β -yl propionate (CCXCII)

The oil, O_5 analysed for $C_{34}H_{58}O_4$. It is evident from the composition that acetic acid has been added across the double bond. The i.r. spectrum gave a strong and broad band at 1735 cm^{-1} which may be due to two carbonyls, one of acetate and another of propionate function; C-O stretching was recorded at 1230 cm^{-1} . The n.m.r. spectrum of the compound gave a broad signal merged with a sharp signal at δ 4.55 integrating for two protons, which was assigned to the C_3 and C_6 protons as in the structure (CCXCII). The broad signal was assigned to C_3 - αH (axial) and the sharp signal with half band width 3 Hz to C_6 - αH (equatorial). This suggested that acetate at C_6 is axial (β -oriented). A distorted quartet at δ 2.1 integrating for two protons was assigned to the α -methylene protons of the propionate and a singlet at δ 2.0 integrating for three protons was due to methyl protons of C_6 acetate. Other methyl protons were recorded at δ 1.2, 1.1, 0.9, 0.8 and 0.7. These spectral values supported the structure (CCXCII) for the oil O_5 .

Characterization of the compound m.p. 176° as 3 β -propionoxy-5 β -hydroxystigmastan-6 α -yl acetic acid γ -lactone (CCXCIII)

The compound m.p. 176° analysed for $C_{34}H_{56}O_4$. The composition was further supported by its mass spectrum which gave molecular ion peak at m/z 528 ($C_{34}H_{56}O_4$).

The i.r. spectrum of the compound m.p.176° gave bands at 1765, 1725 and 1235 cm^{-1} ; band at 1765 was assigned to the carbonyl of the γ -lactone and 1725 to the carbonyl of the propionate; C-O stretching was recorded at 1235 cm^{-1} . On the basis of the composition and i.r. values we may write the possible structures as (CCXCIII and CCXCV-CCXCVII) for the compound m.p.176°.

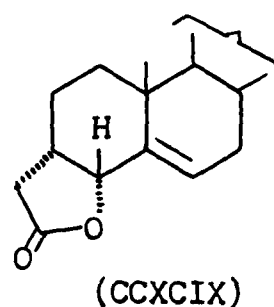
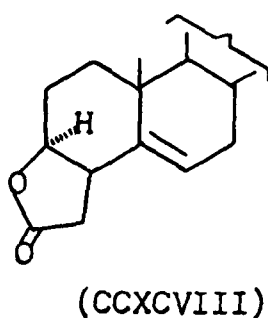
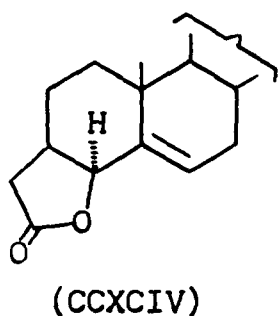


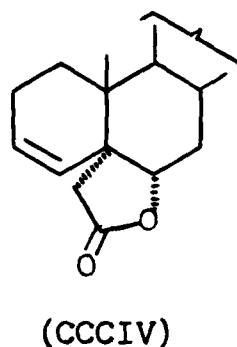
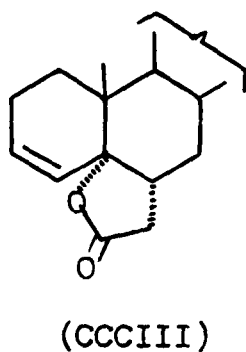
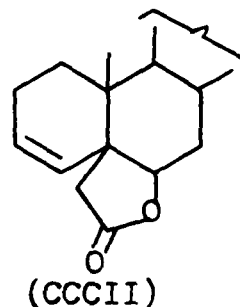
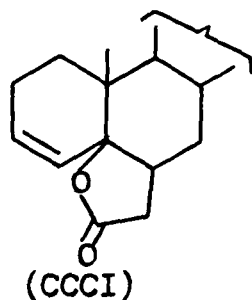
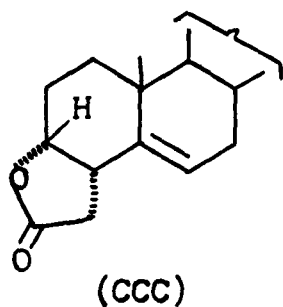
The n.m.r. spectrum of the compound gave a broad signal at δ 4.85 ($W_{1/2}=6$ Hz) integrating for one proton which was assigned to the $C_3-\alpha H$ (equatorial; ring junction A/B cis)¹²⁷. This rules out the possibility of structures (CCXCVI) and (CCXCVII) which have trans A/B ring junction. The absence of a signal for C_6 -proton as in structure (CCXCV) discarded its possibility. Other peak at

δ 2.3 as broad singlet for two protons was assigned to the methylene protons of the lactone moiety. A distorted quartet merged with a singlet at δ 2.3 integrating for two protons was assigned to the methylene protons of the propionate function. Methyl protons were recorded at δ 1.2, 1.16, 1.0, 0.8 and 0.7. These spectral values supported the structure (CCXCIII) for the compound m.p.176°. On the basis of the above discussion the compound m.p.176° may be characterized as 3 β -propionoxy-5 β -hydroxystigmastan-6 α -yl acetic acid γ -lactone (CCXCIII).

Characterization of the compound m.p.95° as 4 β -hydroxystigmast-5-en-3 β -yl acetic acid γ -lactone (CCXCIV)

The compound m.p.95° analysed for C₃₁H₅₀O₂. The i.r. spectrum of the compound gave bands at 1775 and 1650 cm⁻¹ which were assigned to the γ -lactone carbonyl and C=C frequencies, respectively. The C-O stretching was recorded at 1230 cm⁻¹. The i.r. values showed the presence of γ -lactone moiety and a C=C. On the basis of the elemental analysis and i.r. values the possible structures that may be written for the compound m.p.95° are (CCXCIV and CCXCVIII-CCCIV).

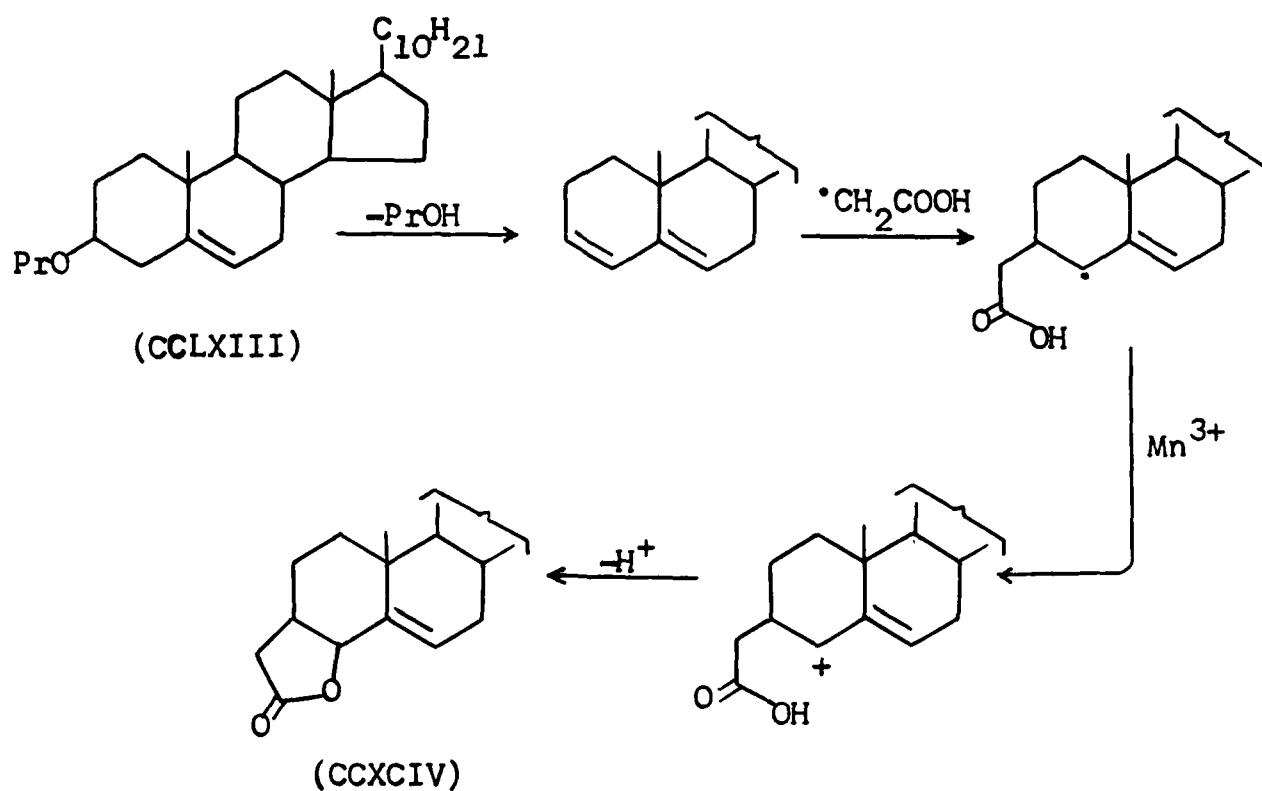




The n.m.r. spectrum of the compound displayed a multiplet at δ 6.05 integrating for one proton which was assigned to the C_6 vinylic proton. This discarded the possibility of structures (CCCI-CCCIV) which have two vinylic protons. A doublet at δ 5.33 ($J=8$ Hz) for one proton was assigned to the C_4 - αH (pseudo equatorial). Its downfield shift is attributed to the fact of being allylic in nature. This again discarded the possibility of structures (CCXCVIII and CCC) which do not have allylic hydrogen attached to an electronegative group. Now the choice is narrowed down to the structures (CCXCIV) and (CCXCIX). The presence of C_5 - C_6 double bond renders ring A to be in a quasi chair form, thus making C_4 - αH pseudo equatorial. The structure (CCXCIX) was discarded because here C_4 - H is β (pseudo axial). A two proton

signal at δ 2.43 (broad) was assigned to the methylene protons of the lactone moiety. Methyl protons were recorded at δ 1.2, 1.06, 0.9, 0.8 and 0.7. These spectral values supported the structure (CCXCIV). The formation of the compound (CCXCIV) may be proposed as shown in scheme-22.

Scheme - 22



On the basis of the spectral values and above discussion the compound m.p. 95° may be characterized as 4 β -hydroxystigmast-5-en-3 β -yl acetic acid γ -lactone (CCXCIV).

MASS SPECTRAL STUDIES ON STEROIDAL COMPOUNDS

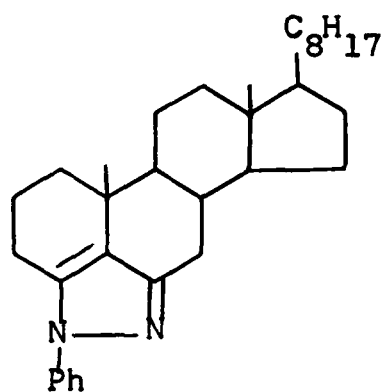
A. Steroidal pyrazoles

A survey of the literature revealed that no systematic mass spectral study of pyrazoles has been reported. In the previous chapter we have described the preparation of a number of steroidal pyrazoles. These two events prompted us to examine the mass spectra of several structurally related steroidal pyrazoles. These included 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI), 2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXL), 2'-phenyl-2,4-cholestadieno[4,6-cd]-pyrazole (CCXXXIII), 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV), 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII), 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole-3-one phenyl-hydrazone (CCXXXVII) and 6-oxo-5 α -3-cholesteno[3,4]-N,N-phenylhydrazine (CCXXXV).

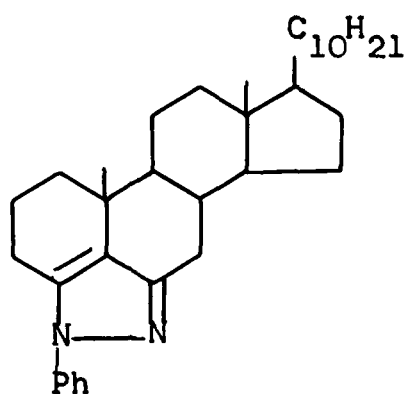
These compounds are structurally very close to each other. It was anticipated that they will follow similar fragmentation pattern thus offering a simple and effective method for their characterization by mass spectrometry. It is gratifying to note that this indeed seems to be the case.

The suggested fragmentation pathways get support from the compositions of the important ions and in some cases by appropriate metastable peaks. However, in the absence of mass spectra of appropriate deuterated analogues the suggested mechanisms

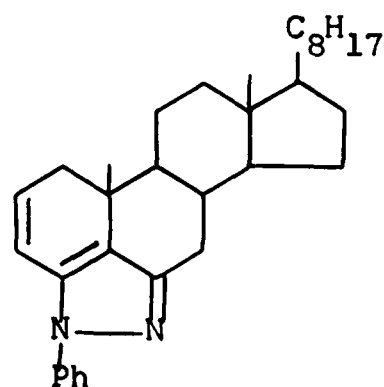
of fragmentation remain tentative, though substituents in some cases compensate this deficiency to some extent.



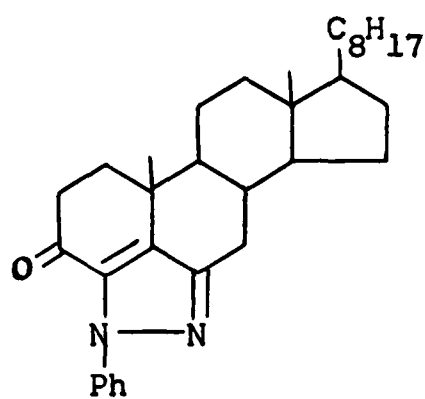
(CCXXI)



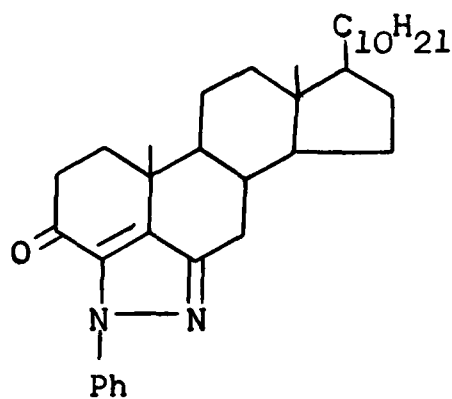
(CCXL)



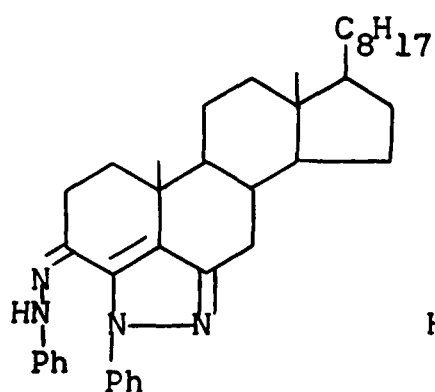
(CCXXXIII)



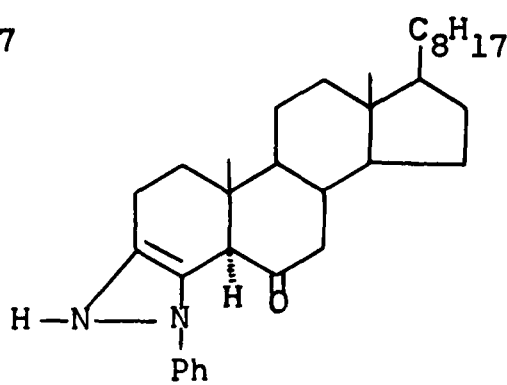
(CCXXV)



(CCXLII)



(CCXXXVII)



(CCXXXV)

Only the mass spectrum of 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI) has been discussed in some detail and this may be considered as the representative model for the pyrazoles (CCXL), (CCXXXIII), (CCXXV), (CCXLII) and (CCXXXVII); the hydrazine (CCXXXV), being so different, has been considered in isolation.

The mass spectrum of 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI) (Fig. 1) gave a very prominent molecular ion peak at m/z 472 ($C_{33}H_{48}N_2$). Other significant ion peaks were observed at m/z 471 (M-H), 457 (M-CH₃), 456, 387 (M-C₆H₁₃), 359 (M-C₈H₁₇ side chain), 345, 344 (m/z 359-CH₃), 332 (M-140), 331, 318 (M-154), 317 (m/z 318-H), 303 (m/z 318-CH₃), 263, 261, 249, 247, 225 ($C_{15}H_{17}N_2$), 224 ($C_{15}H_{16}N_2$), 211 ($C_{14}H_{15}N_2$), 210 ($C_{14}H_{14}N_2$), 209 (m/z 224-CH₃), 195 (m/z 210-CH₃), 147 (m/z 224-C₆H₅), 133 (m/z 210-C₆H₅) and lower mass peaks.

The formation of the more interesting and important ions have been suggested in the following schemes.

m/z 471 (M-H) and m/z 456 (m/z 471-CH₃)

The ion m/z 471 obviously arises by the loss of one hydrogen from the molecular ion. The loss of hydrogen may involve one of the methylene hydrogens either at C₃ or C₇. As pointed out earlier this suggestion does not have the support of mass spectrum of appropriate deuterated analogues.

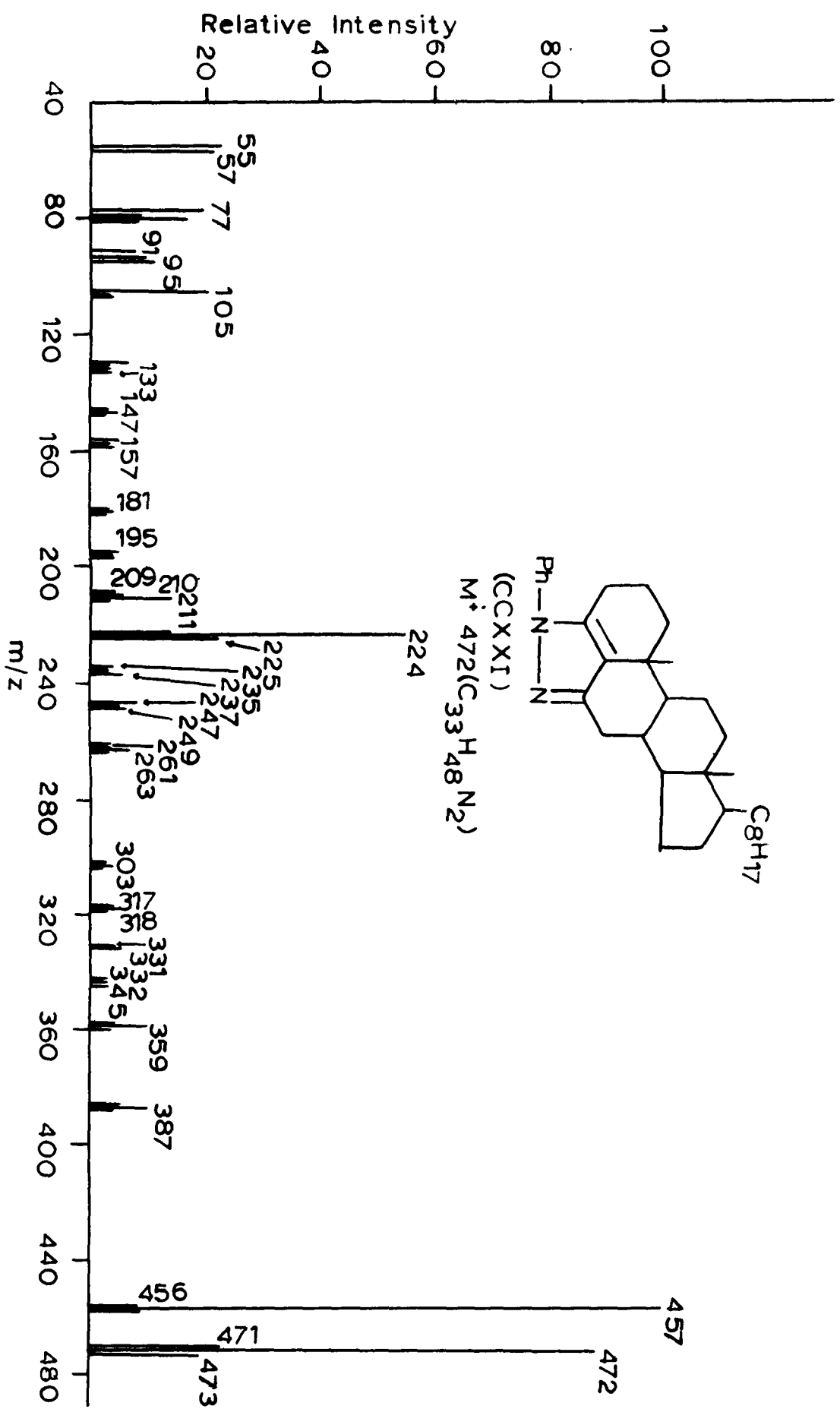
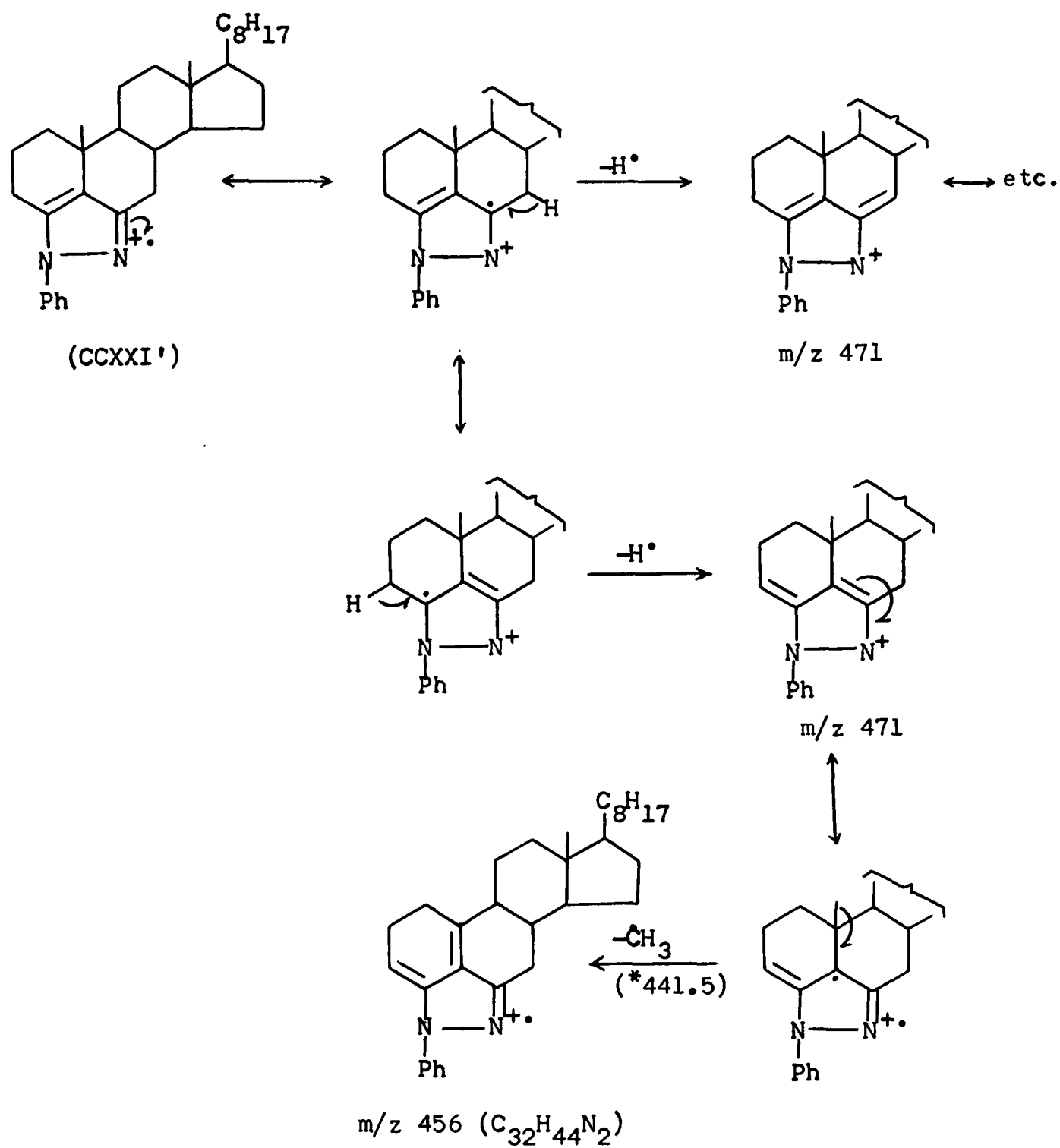


Fig. 1

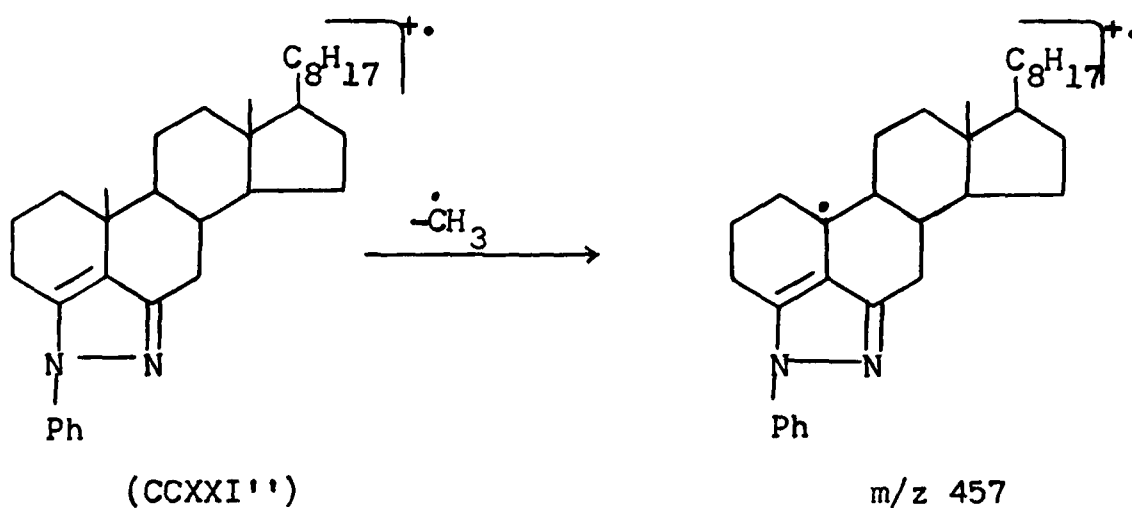
Scheme - 1



m/z 457 (M-CH₃)

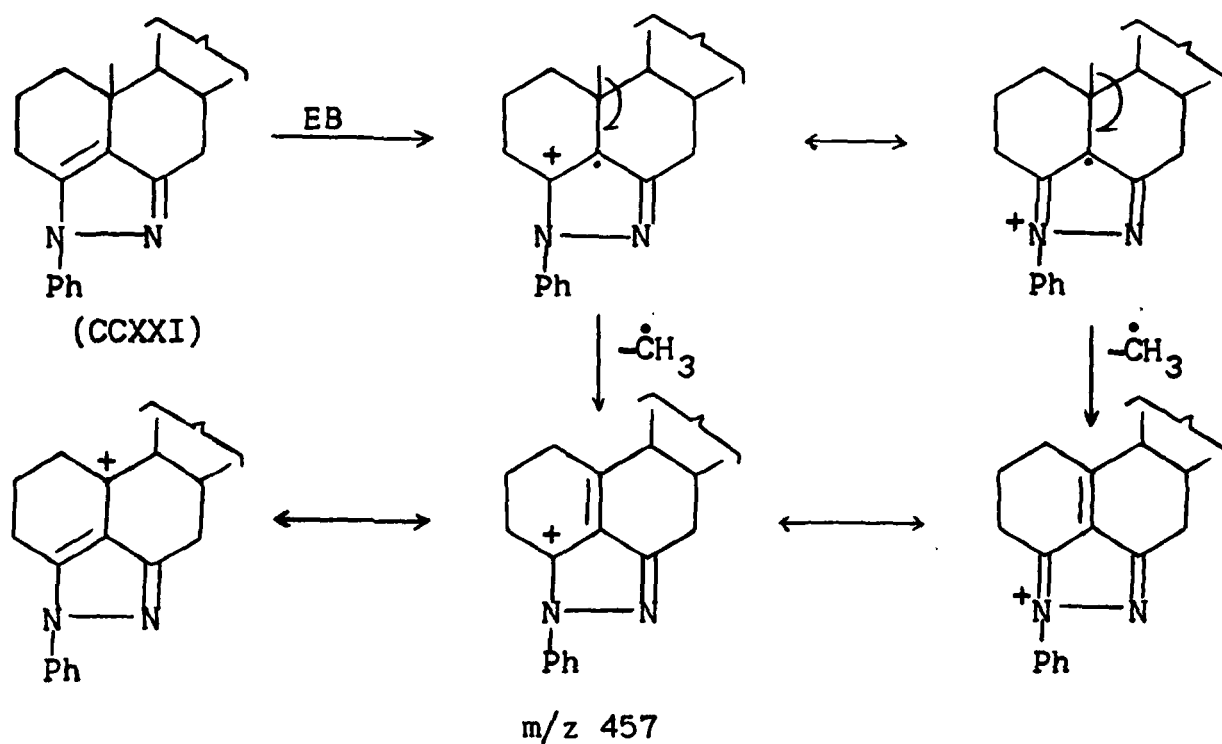
The fragment ion m/z 457 corresponds to the loss of a methyl group from molecular ion. Its composition (C₃₂H₄₅N₂) and a metastable peak at 442.5 fully support this view. In a simple way the loss involving C₁₀-Me group, which is allylic to C₄-C₅ double bond, can be shown according to the scheme-2.

Scheme - 2



The ion peak at m/z 457 constitutes the base peak of the spectrum. Most probably the loss involves the expulsion of C₁₀-methyl group in a major way. The loss of a methyl group, in view of the intensity of the ion peak at m/z 457, can be more elaborately explained as in scheme-3.

Scheme - 3

m/z 387 (M-85)

The ion m/z 387 corresponds to the loss of the mass unit 85 (C_6H_{13}) from the molecular ion. The C_6H_{13} unit may be derived from the side chain. The loss of C_6H_{13} from the side chain is not a matter of regular observation.

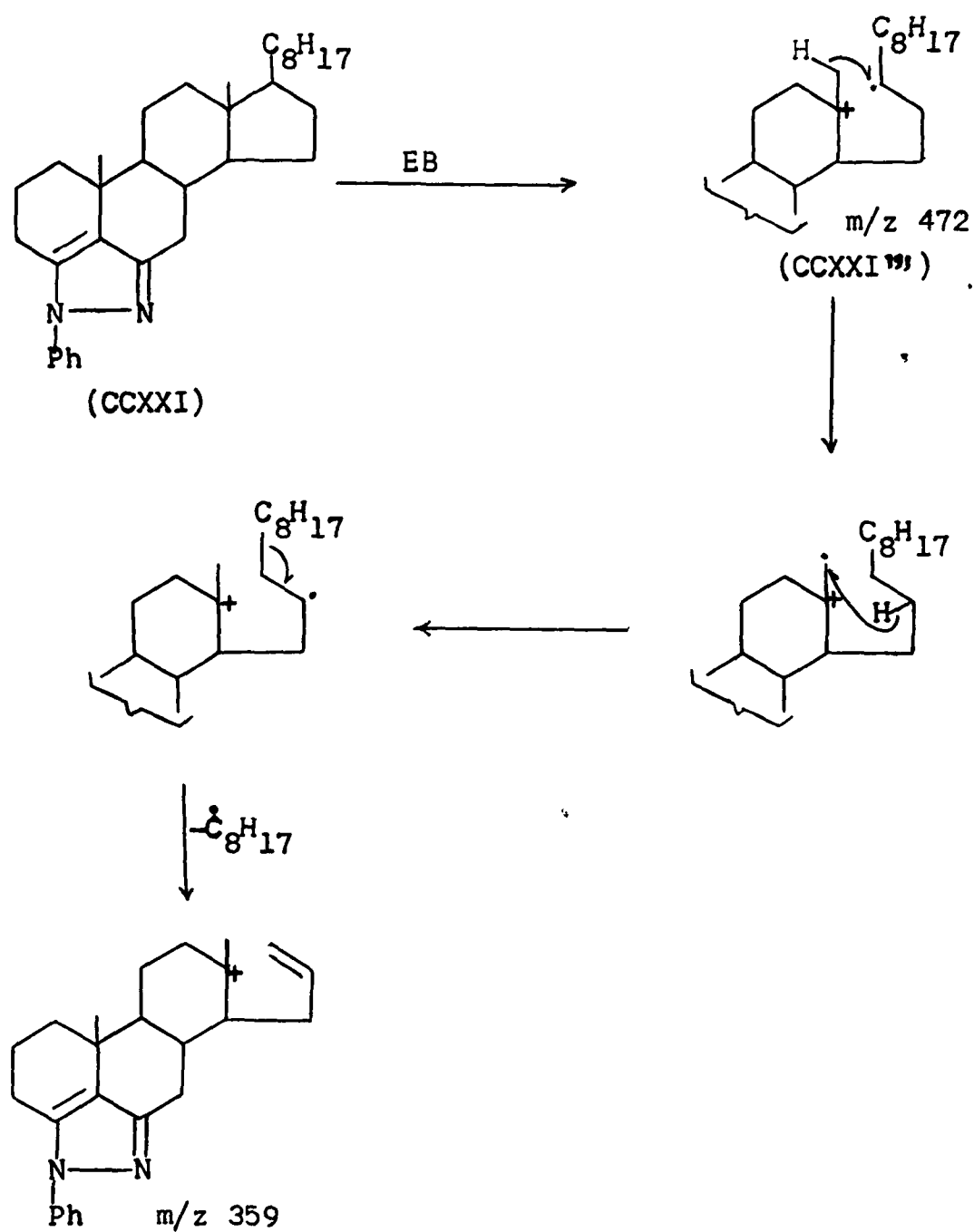
m/z 359 (M- C_8H_{17} side chain)

The loss of the side chain (C_8H_{17}) is of regular occurrence in the mass spectra of steroidal compounds belonging

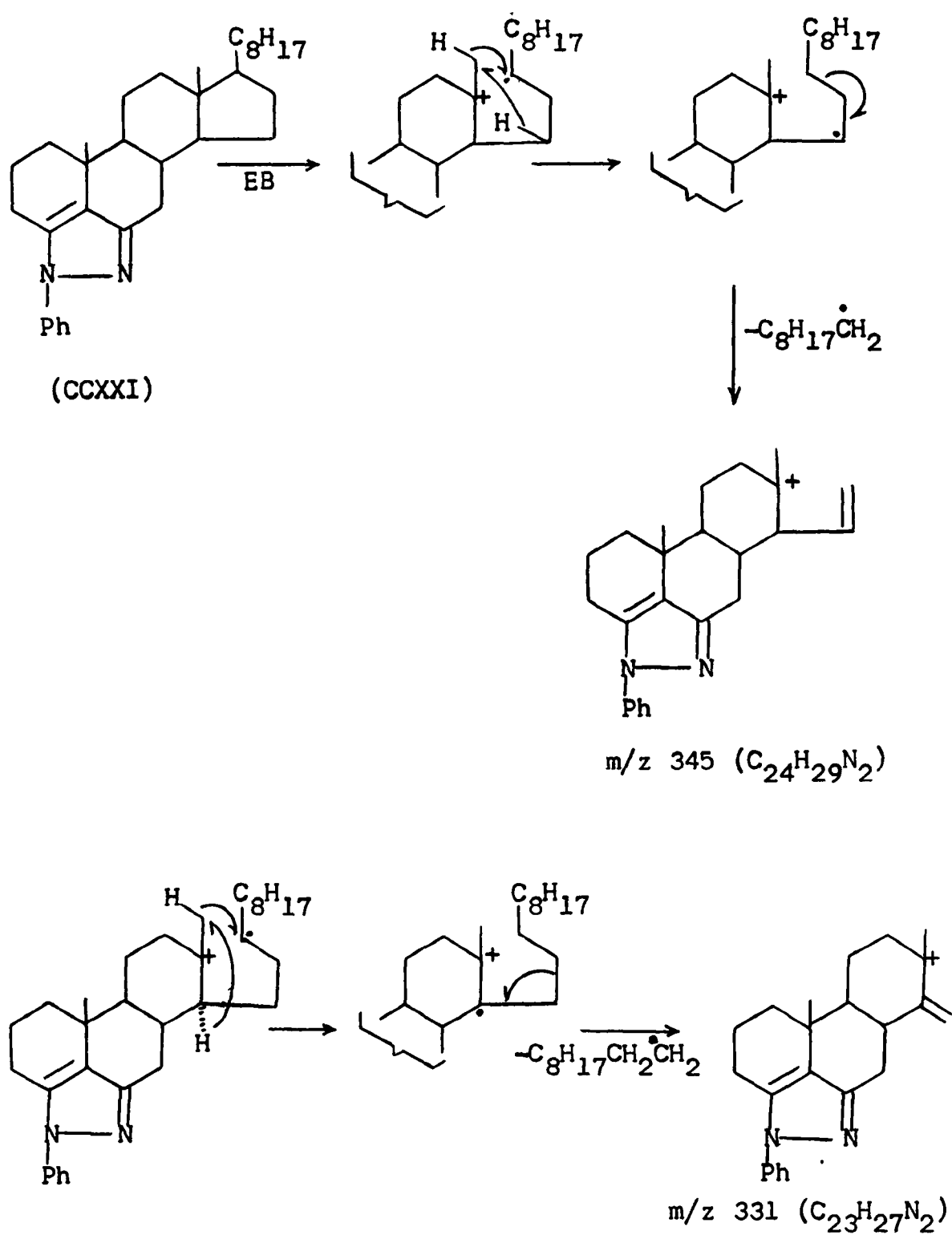
to the cholestane series. In the present case two modes can be suggested.

A. Hydrocarbon directed fragmentation

Scheme - 4



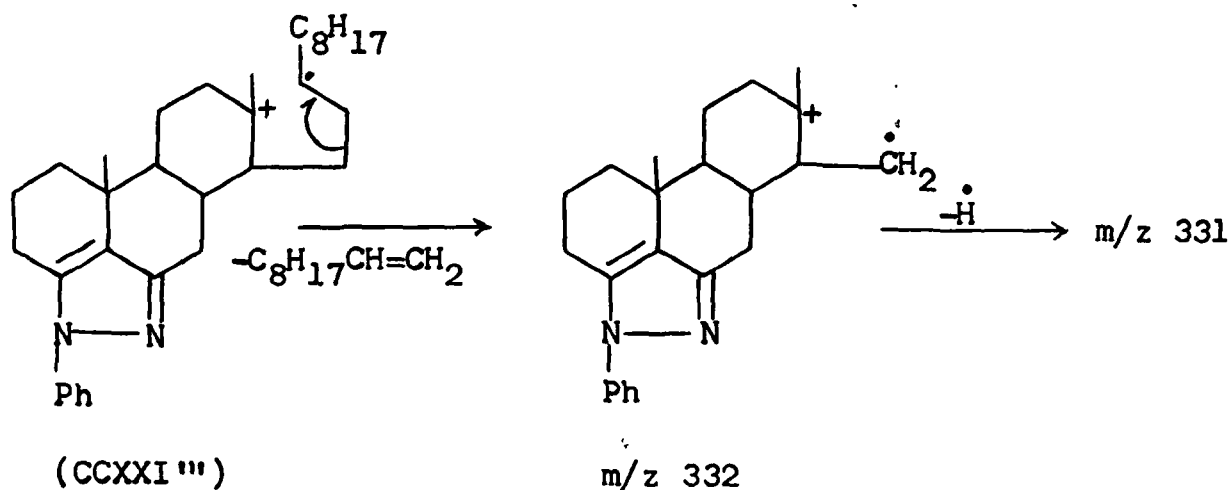
Scheme - 6



m/z 332 ($C_{23}H_{28}N_2$)

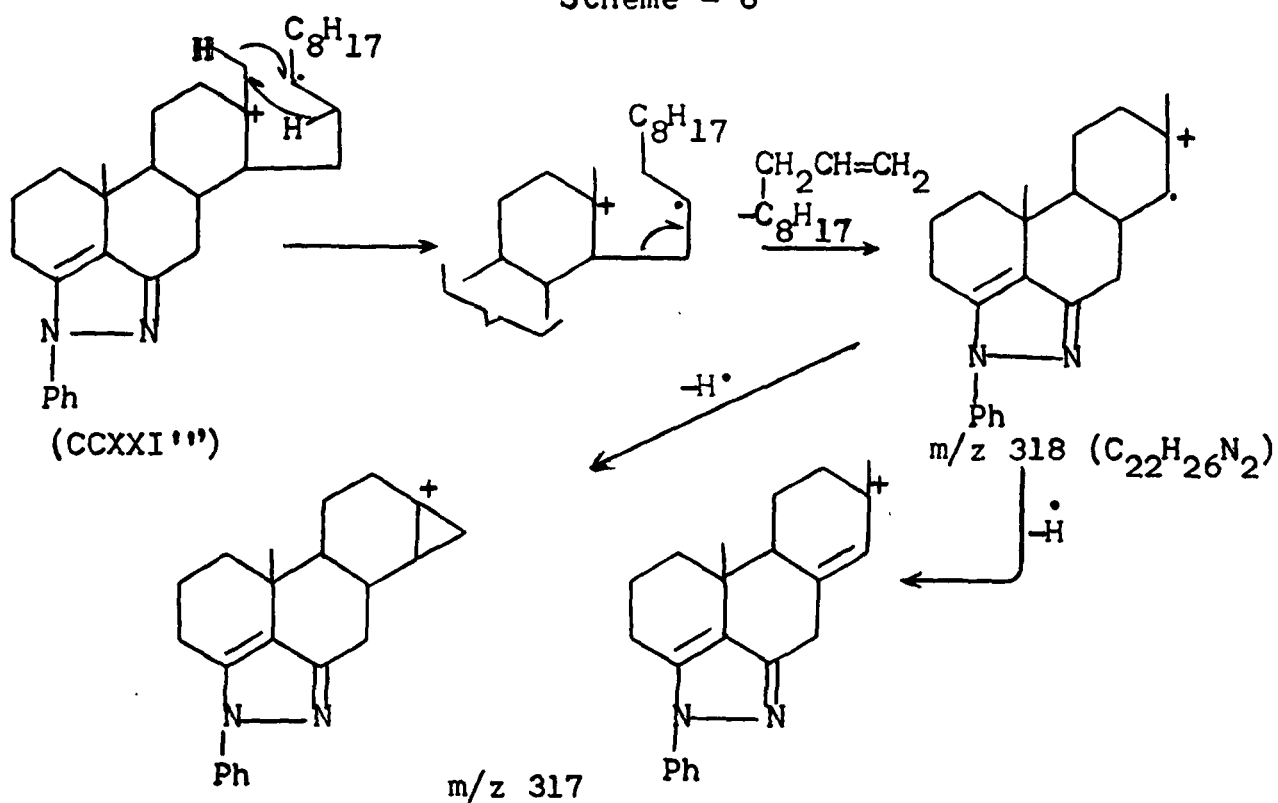
The ion m/z 332 corresponds to the loss of mass unit 140 from the molecular ion. The mass unit 140 is built up of the side chain and a part of ring D (C_{16} and C_{17}). This loss is of common occurrence in the mass spectra of the cholestane derivatives.

Scheme - 7

m/z 318 and 317

These ions are derived from the combined loss of the side chain and ring D (C_{15} , C_{16} and C_{17}) as shown in scheme-8.

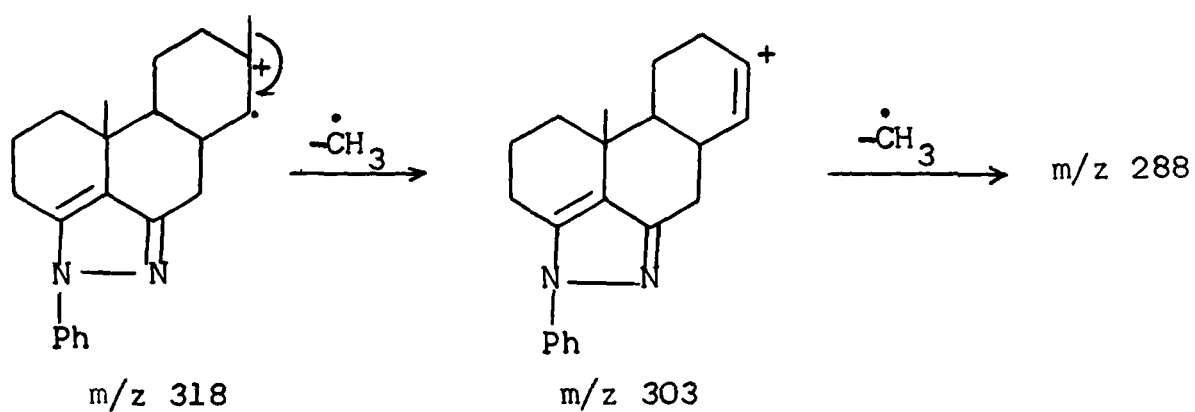
Scheme - 8



$\text{m/z } 303 \text{ (m/z } 318 - \text{CH}_3\text{)}$

The formation of the ion $\text{m/z } 303$ can be shown to arise by the loss of a methyl group from the ion $\text{m/z } 318$

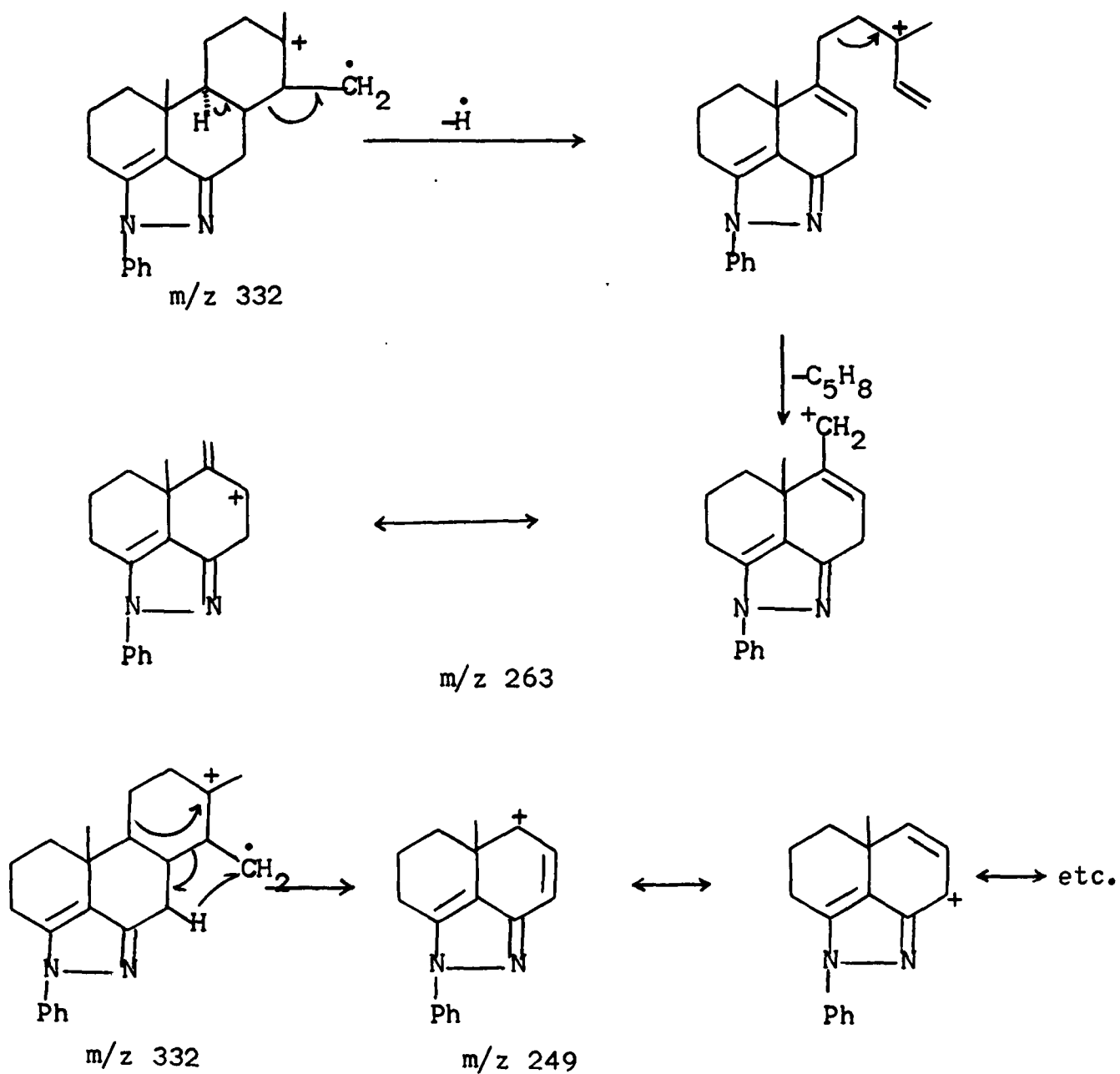
Scheme - 9



m/z 263 ($C_{18}H_{19}N_2$) and m/z 240 ($C_{17}H_{17}N_2$)

The formation of these important homologous ions can be shown according to scheme-10. The precursor of these ions is most likely the ion m/z 332.

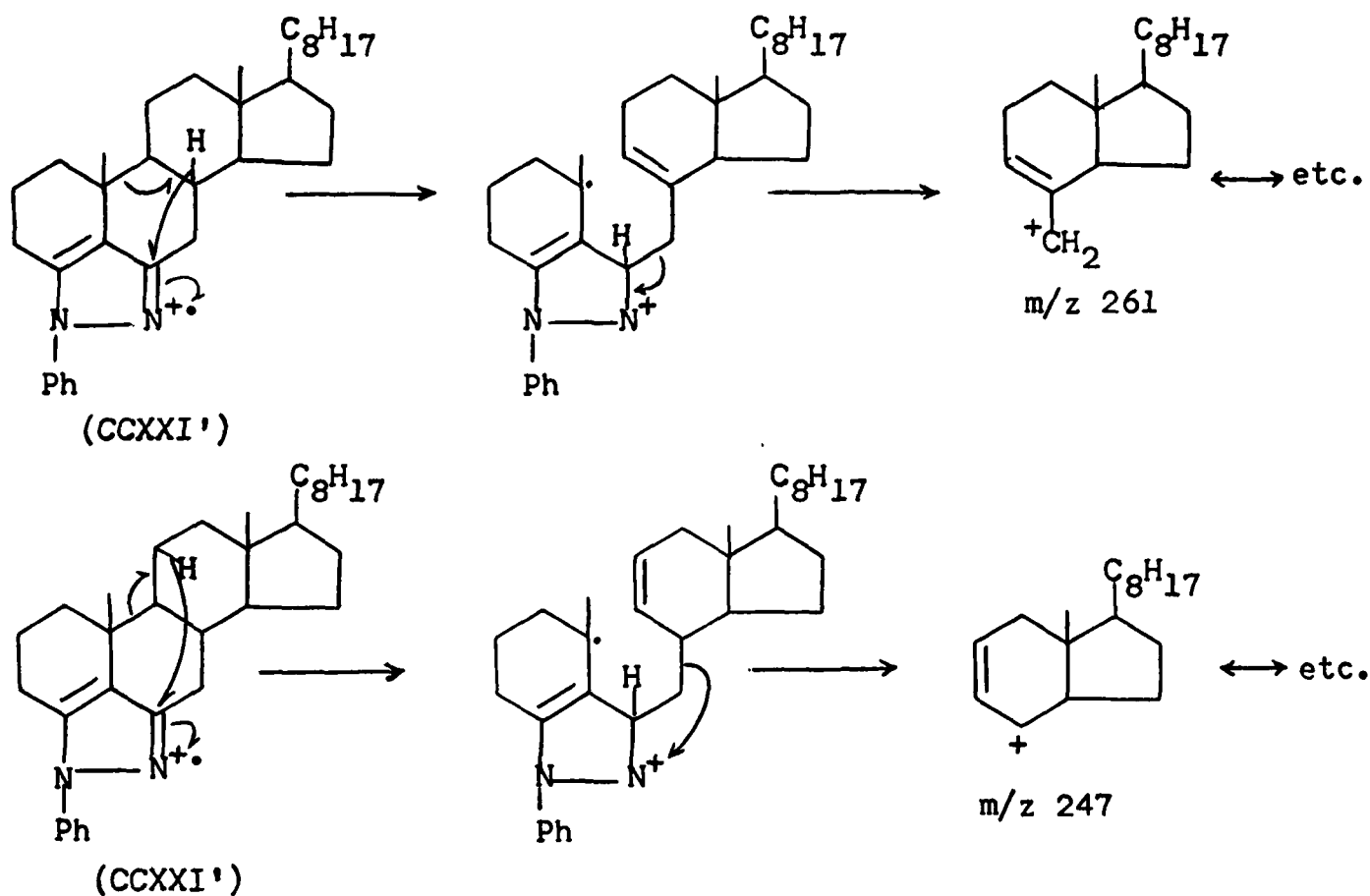
Scheme - 10



m/z 261 ($C_{19}H_{33}$) and 247 ($C_{18}H_{31}$)

These hydrocarbon ions are of common occurrence in the spectra of the cholestane derivatives. The formation of these ions can be conveniently shown according to scheme-11.

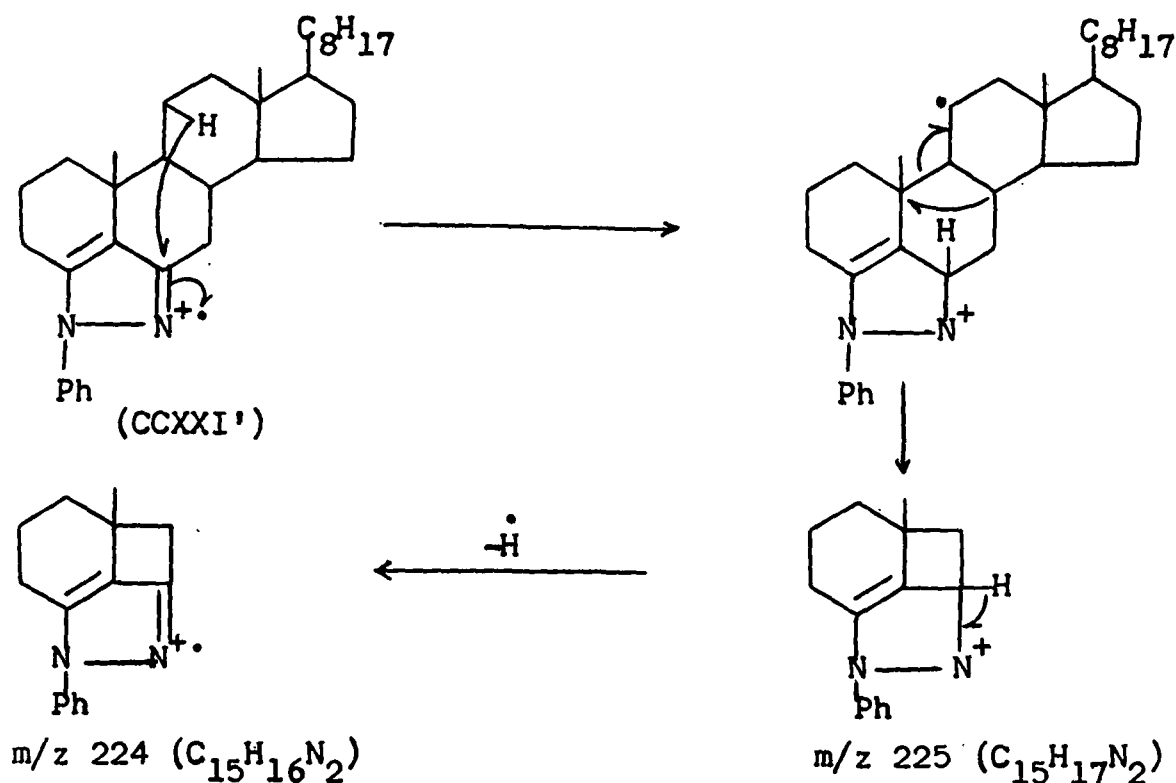
Scheme - 11

m/z 225 and 224

Perhaps the most significant ion peak in the spectrum is m/z 224. Its formation can be shown to occur in more than one

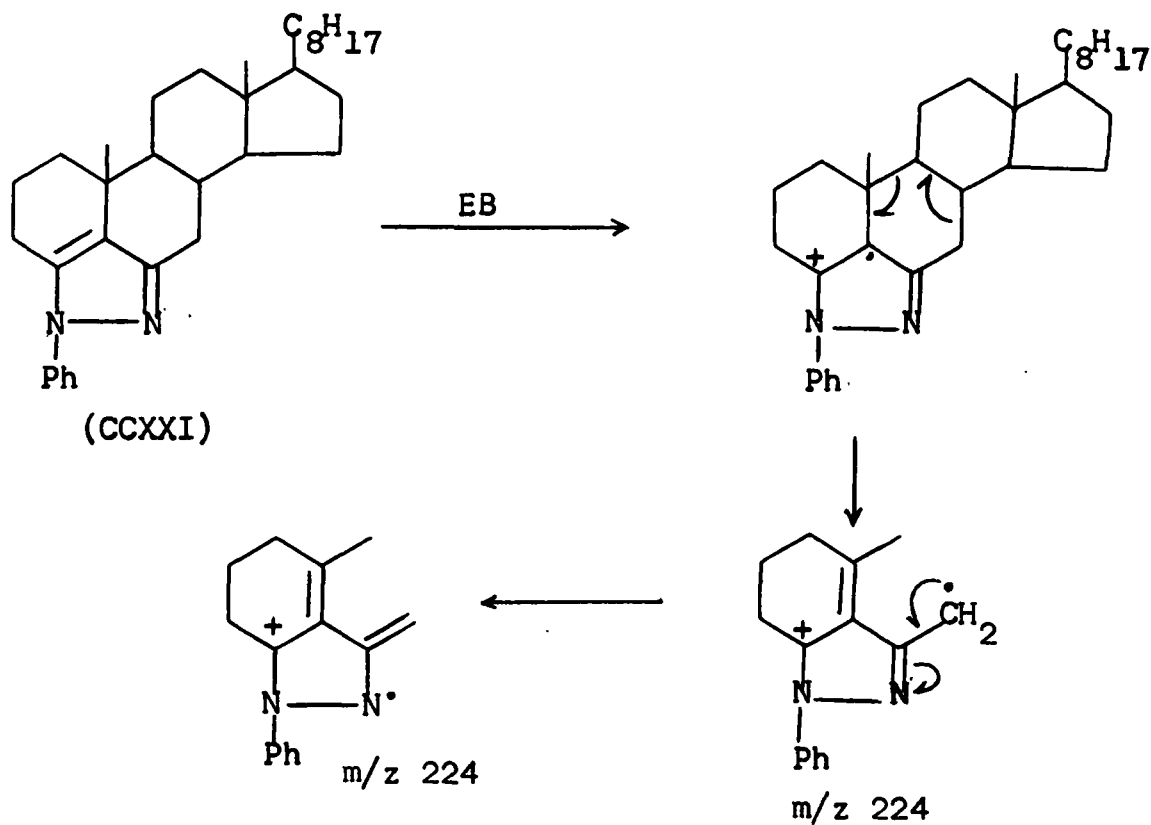
way. One of the possibilities is the involvement of the ion m/z 225 which on one hydrogen loss can give rise to the ion m/z 224.

Scheme - 12



The proposed structure for the ion 224 agrees with the composition $C_{15}H_{16}N_2$. However, it appears doubtful that such a strained structure having a cyclobutane moiety will have stability enough to be accumulated to attain such a high relative abundance. In view of the apparent importance of the ion m/z 224 it was considered desirable to suggest an alternative pathway for its formation. Such an attempt has been made in scheme-13. This suggestion finds support from a metastable peak, though a weak one at m/z 106.

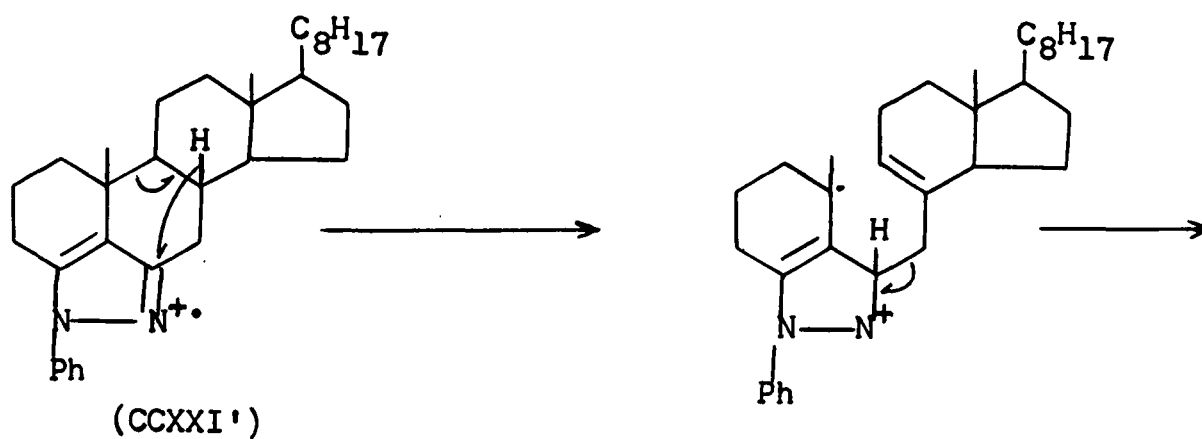
Scheme - 13

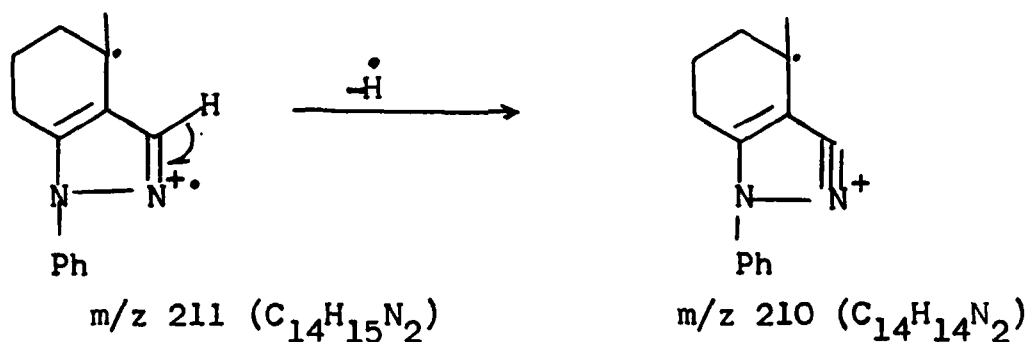


m/z 211, 210 and 209

These important ions, m/z 211 and 210 can be shown to arise according to scheme-14. These ions along with the ion m/z 224 are of diagnostic value.

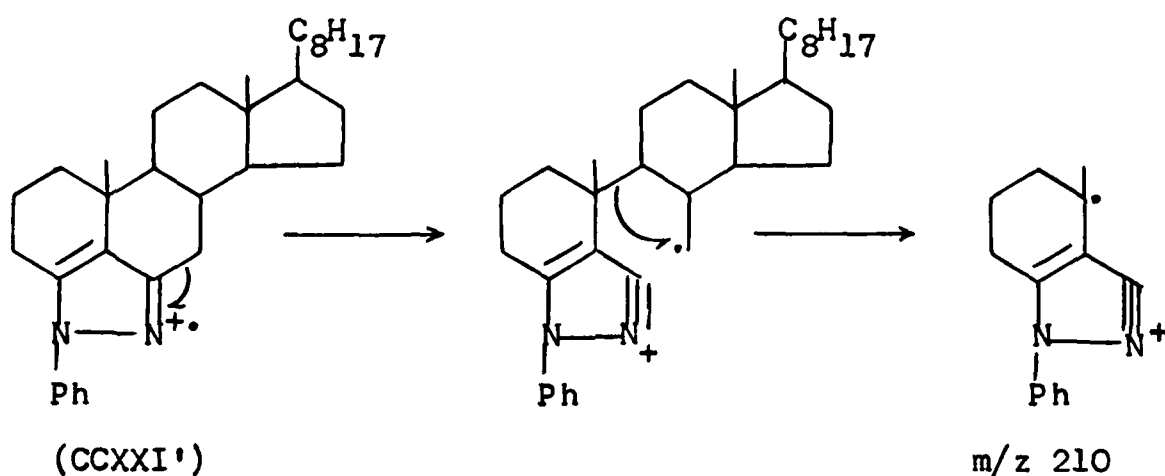
Scheme - 14





Alternatively, the ion m/z 210 can be shown to arise without the involvement of the ion m/z 211.

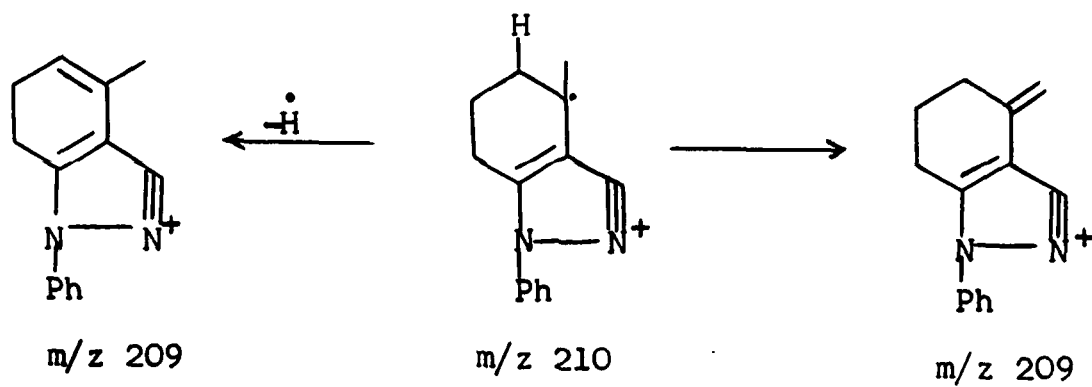
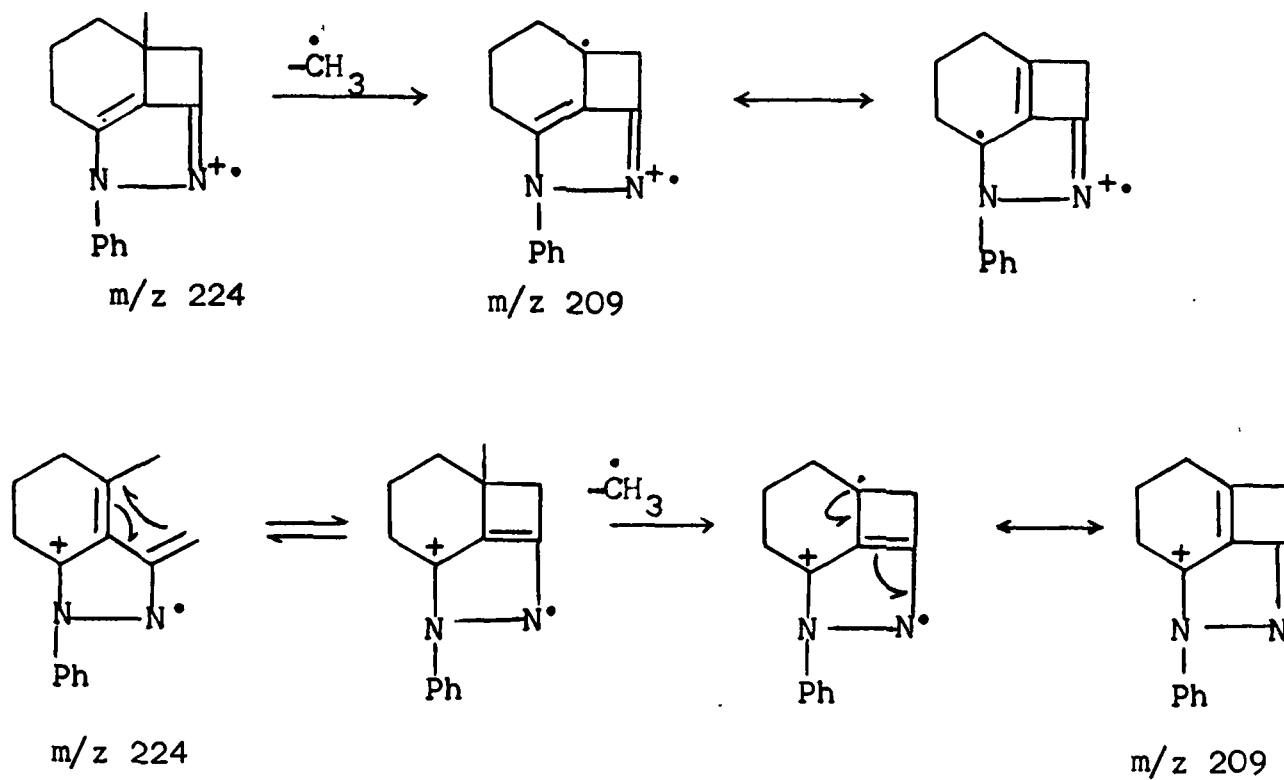
Scheme, - 15



The ion m/z 209 may result either by the loss of one hydrogen from the ion m/z 210 or by the loss of a methyl group from the ion m/z 224.

m/z 210-H

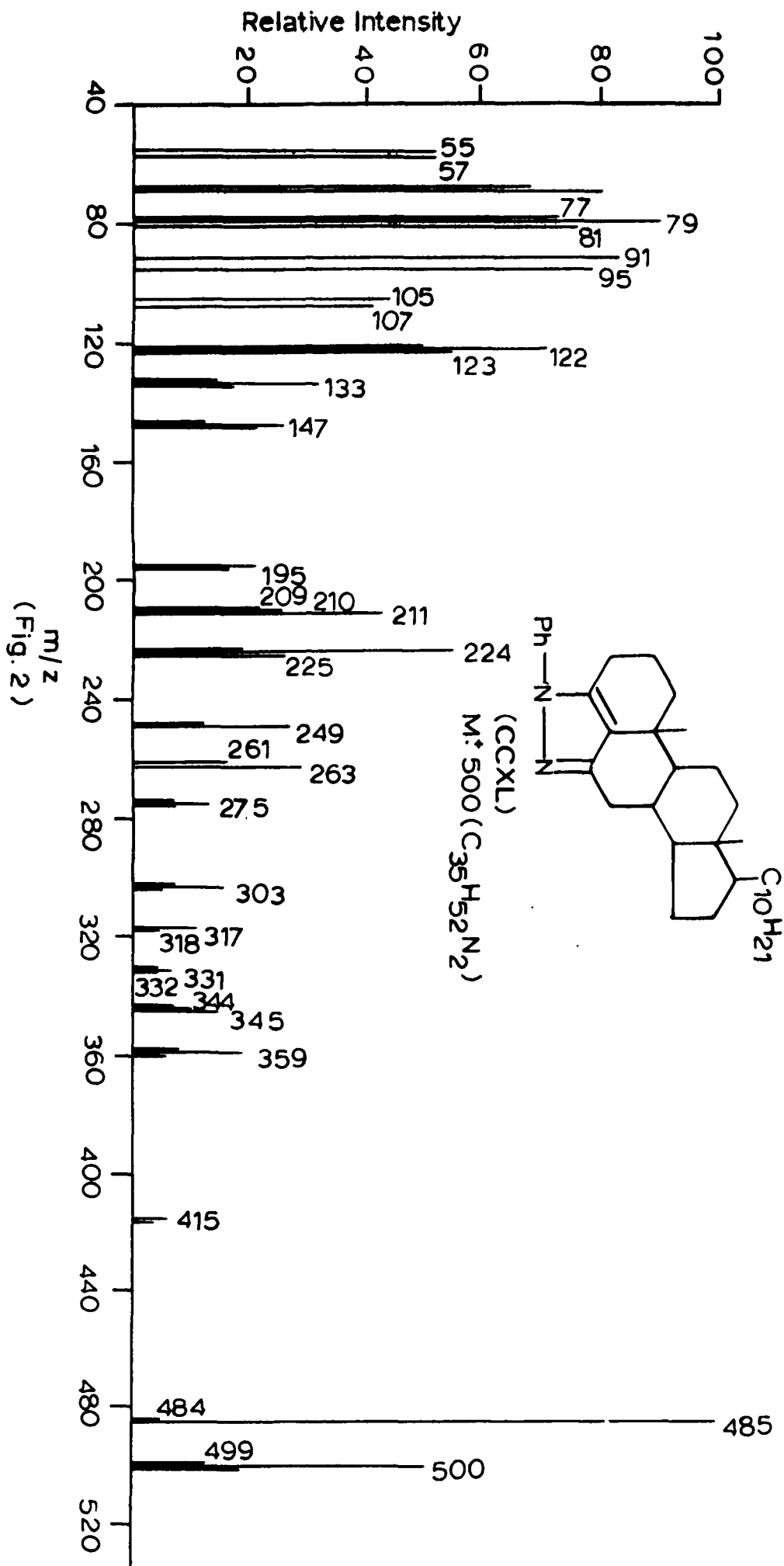
Scheme - 16

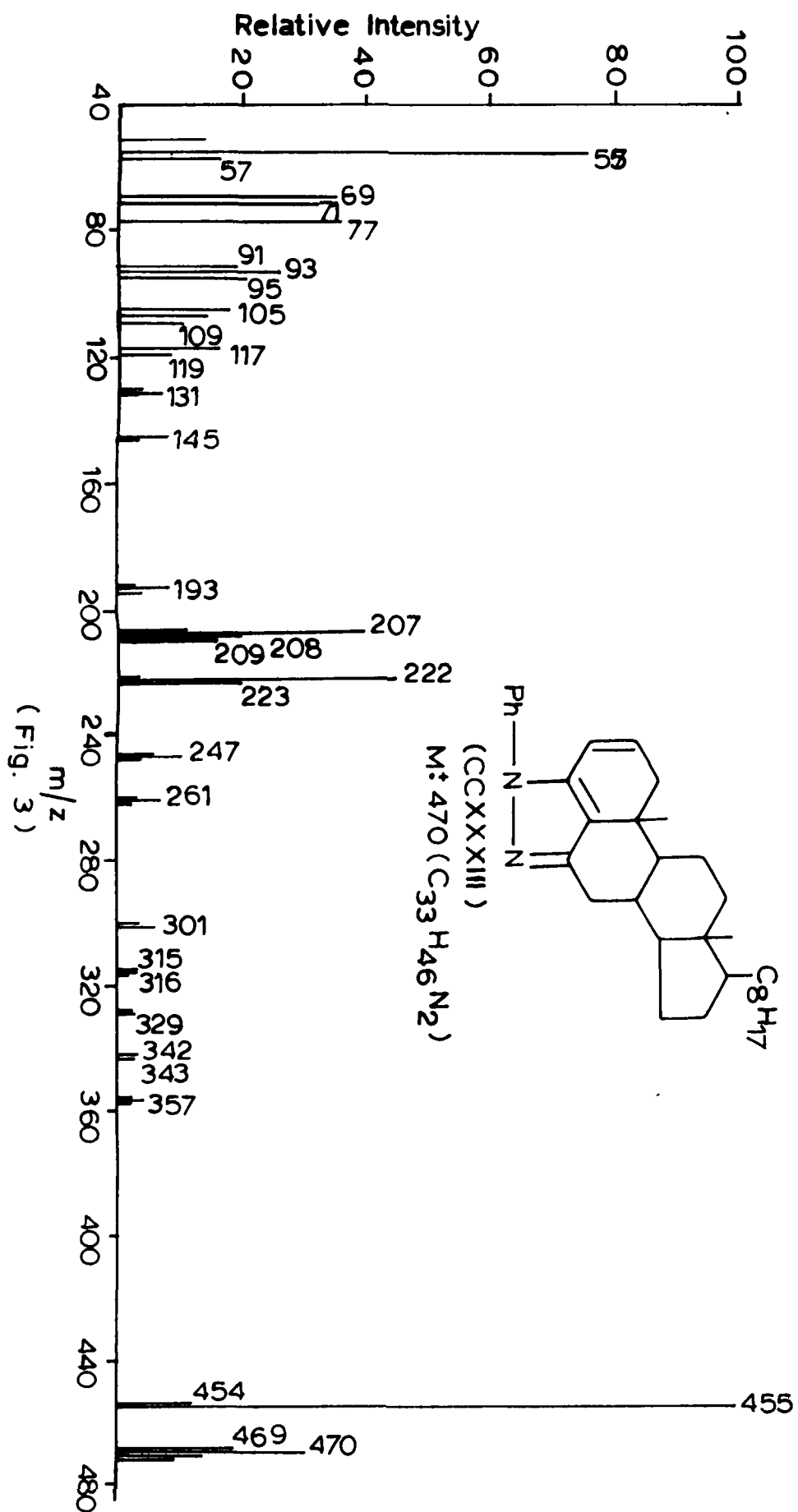
m/z 224-CH₃

The mass spectrum of 2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXL) (Fig. 2) gave a prominent molecular ion peak at m/z 500 ($C_{35}H_{52}N_2$). Other significant corresponding peaks with respect to (CCXXI) were obtained at m/z 499 (M-H), 485 (M-CH₃), 484 (m/z 499-CH₃), 415 (M-85), 359 (M-side chain, $C_{10}H_{21}$), 345 (M-155), 344 (m/z 359-CH₃), 332 (M-side chain and part of ring D), 331 (M-169), 318 (M-side chain and ring D), 317 (m/z 318-H), 303 (m/z 318-CH₃), 275, 263, 261, 249, 225 ($C_{15}H_{17}N_2$), 224 ($C_{15}H_{16}N_2$), 211, 210, 209, 195, 147, 133 and lower mass peaks.

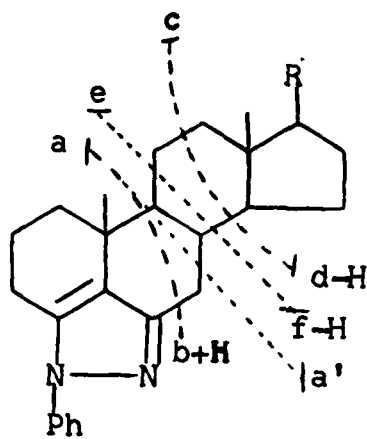
The mass spectrum of 2'-phenyl-2,4-cholestadieno[4,6-cd]-pyrazole (CCXXXIII) (Fig. 3) gave molecular ion at m/z 470 ($C_{33}H_{46}N_2$) along with other significant ion peaks at m/z 469 (M-H), 455 (M-CH₃, base peak), 454, 357 (M-C₈H₁₇ side chain), 343 (M-127), 342 (M-C₈H₁₇ side chain + CH₃), 329 (M-141), 316, 315, 301 (m/z 316-CH₃), 261, 247, 223 ($C_{15}H_{15}N_2$), 222 ($C_{15}H_{14}N_2$), 209, 208, 207 (m/z 222-CH₃), 193 (m/z 208-CH₃), 145 (m/z 222-77), 131 and lower mass peaks.

A comparison of the spectra of these three pyrazoles (Figs. 1-3) clearly showed remarkable similarity between them. These three pyrazoles represent changes in the different parts of the molecules which can be made use of in the interpretation of the spectra. Taking (CCXXI) as the central compound, the pyrazole (CCXL) represents change at the top of the molecule whereas (CCXXXIII) has an additional double bond in ring A.





A screening of these spectra revealed that these steroidal pyrazoles undergo characteristic fragmentation which can be exploited for identification purpose. For the present we recognise 4 cleavage modes as shown in the structure below.



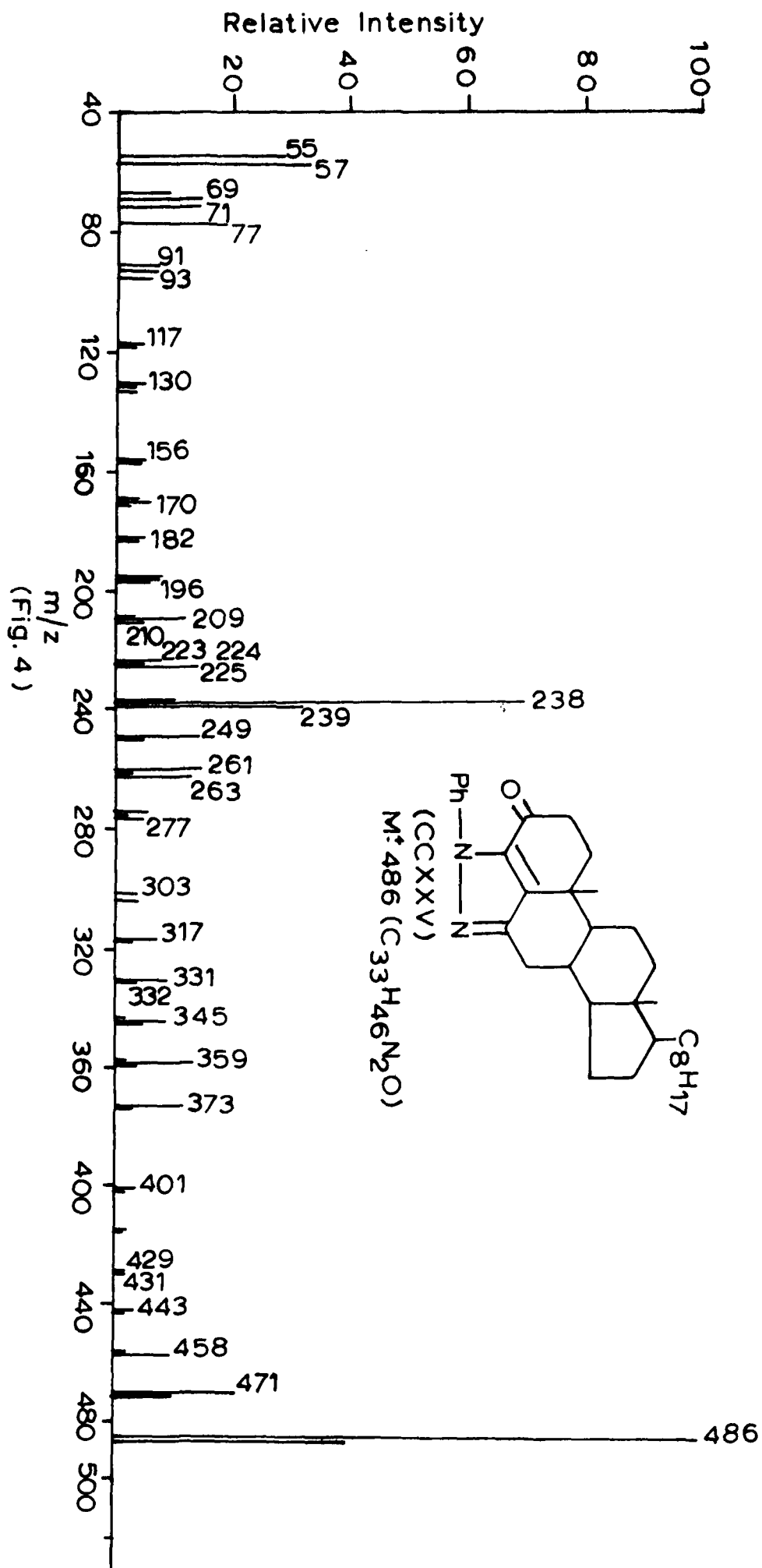
Cleavage mode a-a' leads to the prominent ion m/z 224 ($C_{15}H_{16}N_2$) in (CCXXI) and (CCXL), though they differ in their C_{17} -side chain; (CCXXXIII) having an additional double bond in ring A (C_2-C_3) leads to the ion m/z 222 ($C_{15}H_{14}N_2$). Cleavage mode a-b leads to the ion m/z 211 in the first two cases whereas m/z 209 is obtained from the diene pyrazole (CCXXXIII). Rupture of the ring C (cleavage modes c-d and e-f) give rise to ion m/z 263 and 249, respectively in the compounds (CCXXI) and (CCXL) and ion m/z 261 and 247 in the case of (CCXXXIII). For the reason of prominence we prefer cleavage mode a-a' as the most diagnostic of all the other cleavage modes.

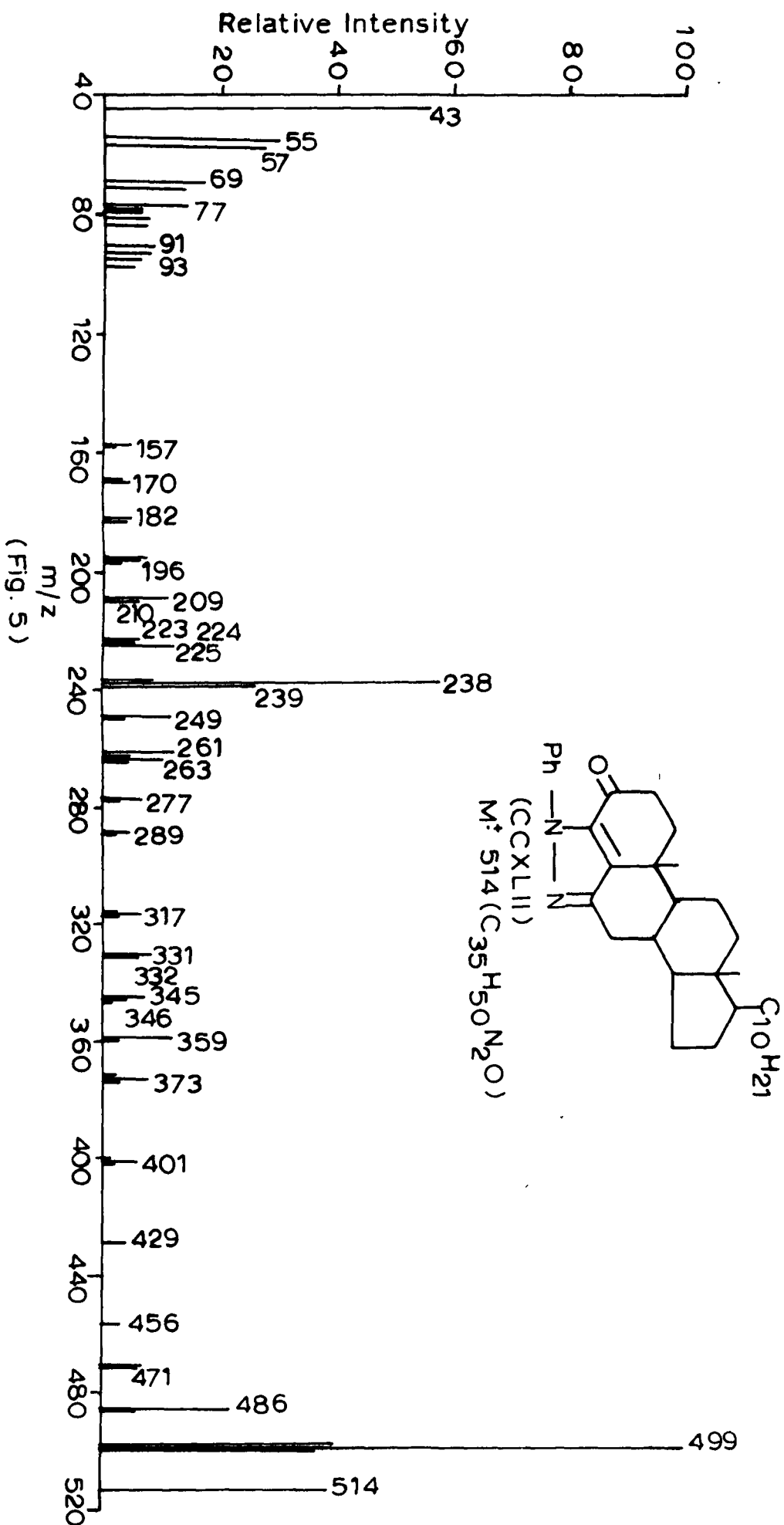
The keto pyrazoles (CCXXV) and (CCXLII) having a keto function at C₃ but differing at C₁₇ with respect to side chain offers the opportunity of testing the conclusions arrived at regarding these cleavage modes.

The mass spectrum of 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV) (Fig. 4) gave molecular ion peak at m/z 486 (C₃₃H₄₆N₂O). Other prominent ion peaks were observed at m/z 471 (M-CH₃), 458 (M-CO), 443 (m/z 458-CH₃), 401 (M-C₆H₁₃), 373 (M-C₈H₁₇ side chain), 359, 346 (M-140), 345, 332 (M-154), 331 (M-155), 317 (m/z 332-CH₃), 277, 263, 261, 249, 239, 238, 225, 224, 223 (m/z 238-CH₃), 210 (m/z 238-CO), 209 (224-CH₃), 196 (m/z 224-CO) and lower mass peaks.

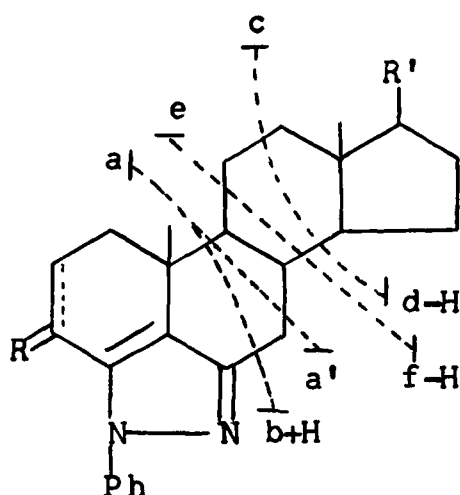
The mass spectrum of 3-oxo-2'-phenyl-4-stigmasteno [4,6-cd]-pyrazole (CCXLII) (Fig. 5) gave molecular ion peak at m/z 514 (C₃₅H₅₀N₂O). The other peaks were observed at m/z 499 (M-CH₃), 486 (M-CO), 471 (m/z 486-CH₃), 429 (M-85), 373 (M-C₁₀H₂₁ side chain), 359, 346, 345, 332, 331, 317, 289, 277, 263, 249, 239, 238, 225, 224, 223, 210, 209, 196 and lower mass peaks.

These two spectra (Figs. 4 and 5) are comparable with those of the non-ketonic pyrazoles (Figs. 1-3) in most of the details. As expected, the loss of CO occurred in (CCXXV) and (CCXLII) at one stage or the other.





As anticipated both the spectra (Figs. 4 and 5) showed cleavage mode a-a' very distinctively giving rise to the ion m/z 238 ($C_{15}H_{14}N_2O$) and equally important are cleavage modes a-b, c-d and e-f. These cleavage modes in the five pyrazoles discussed above have been summed up in the following tabular form.



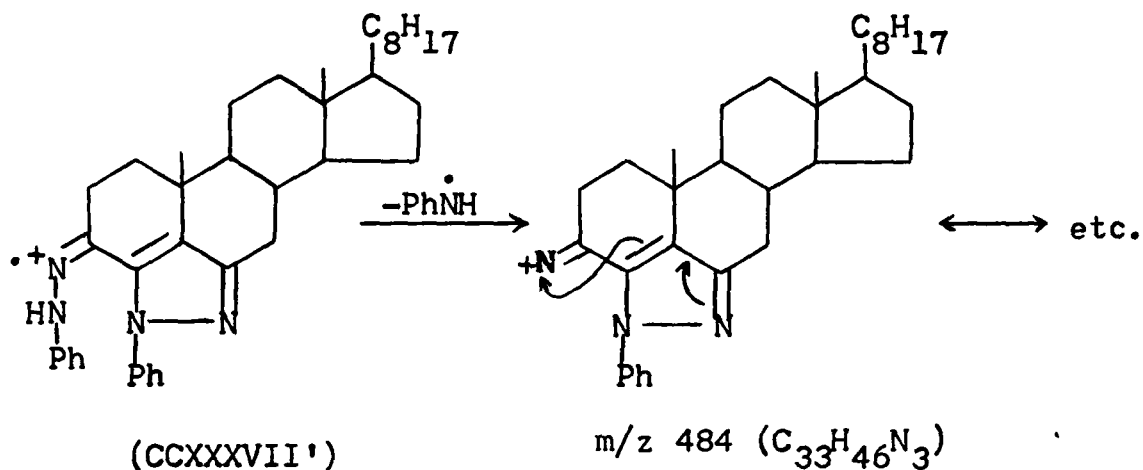
Cleavage Modes

	<u>R</u>	<u>R'</u>	<u>a-a'</u>	<u>a-b+H</u>	<u>c-d-H</u>	<u>e-f-H</u>
(CCXXI)	H ₂	C ₈ H ₁₇	224	211	263	249
(CCXL)	H ₂	C ₁₀ H ₂₁	224	211	263	249
(CCXXXIII)	H					
	(C ₂ =C ₃)	C ₈ H ₁₇	222	209	261	247
(CCXXV)	O	C ₈ H ₁₇	238	225	277	263
(CCXLII)	O	C ₁₀ H ₂₁	238	225	277	263

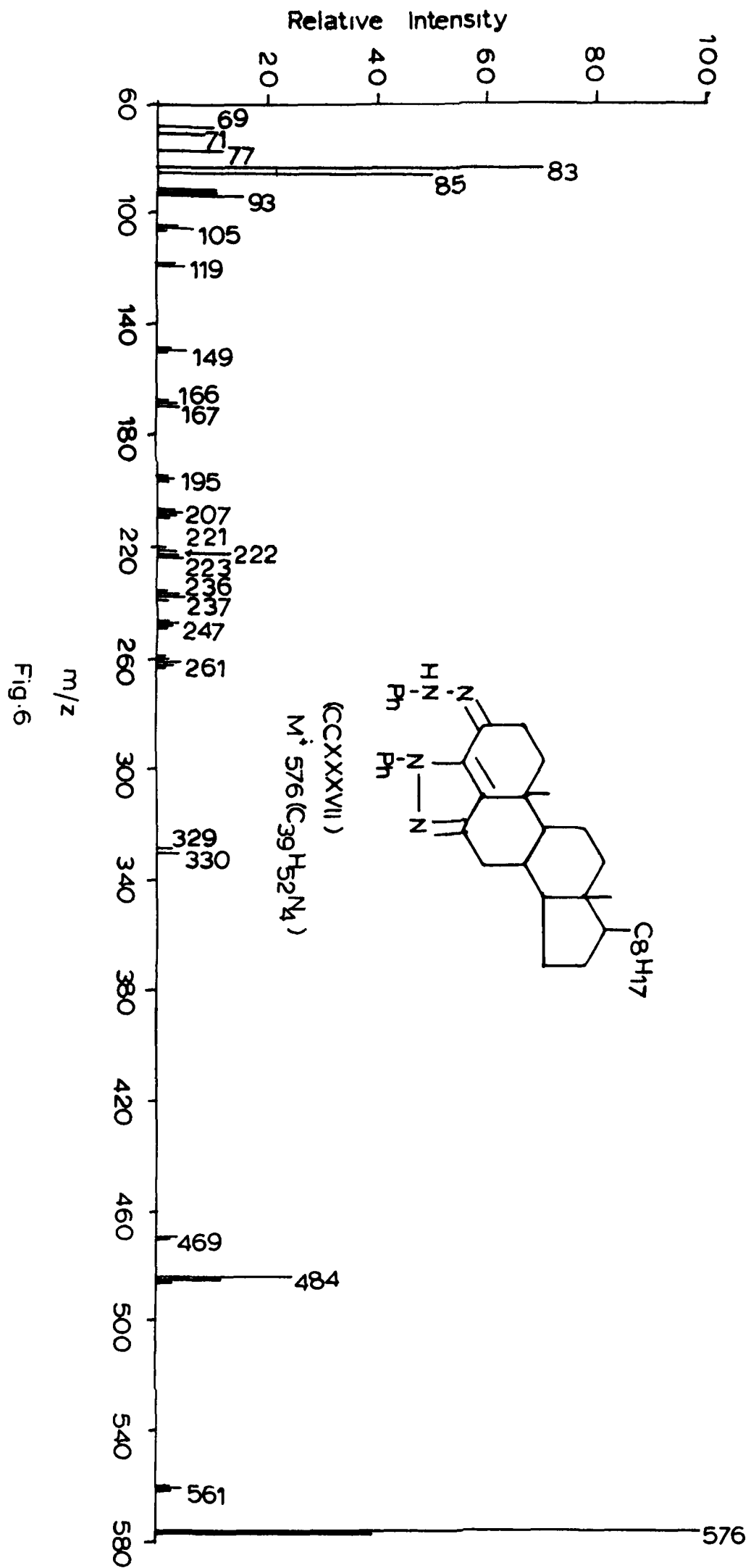
The mass spectrum of 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole-3-one phenylhydrazone (CCXXXVII) (Fig. 6) gave molecular ion peak at m/z 576 ($C_{39}H_{52}N_4$) which happens to be the base peak also. Except for a reasonably strong peak at m/z 484 ($M-NHPh$) all the other peaks are of poor intensity. However, weak peaks were observed at m/z 561 ($M-CH_3$), 469 (m/z 484- CH_3), 330, 329, 261, 247, 237, 236, 223, 222, 221 (m/z 236-15), 207 and lower mass peaks. These peaks can be related with those obtained in the previously discussed spectra.

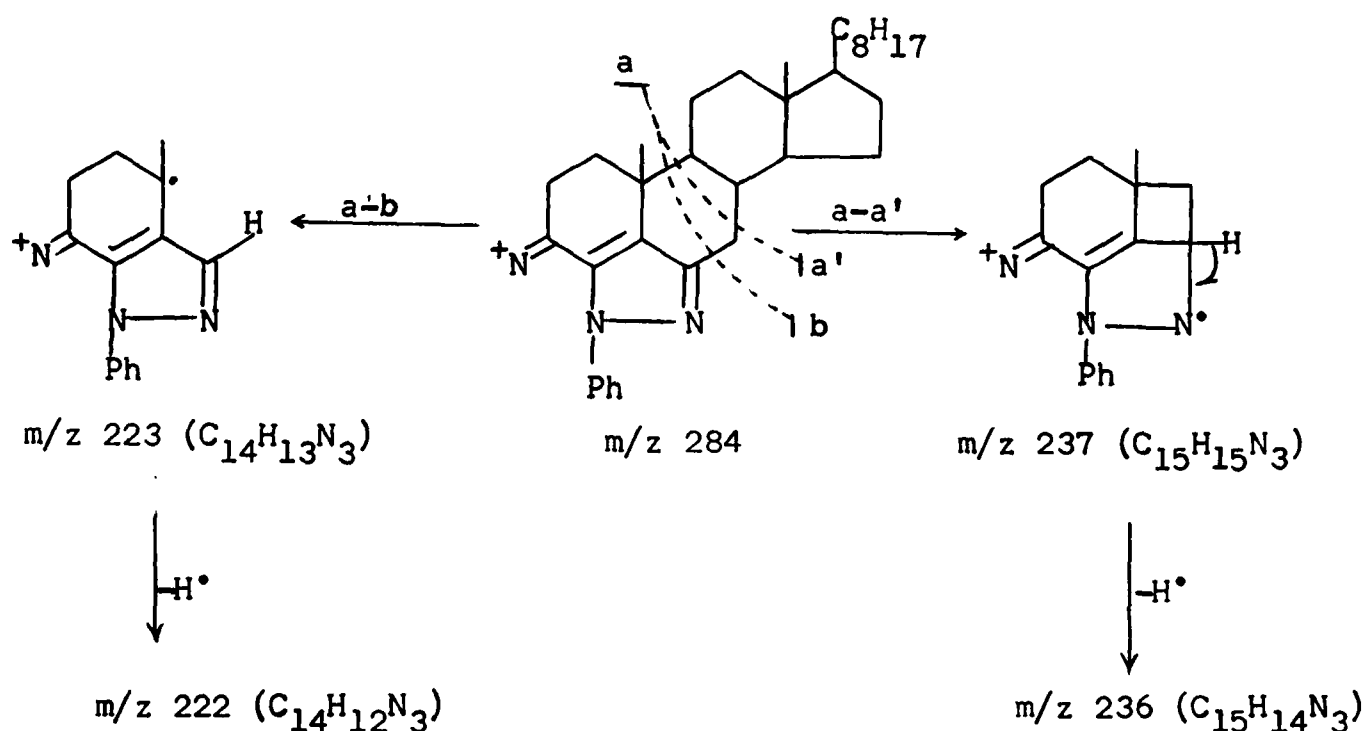
The loss of mass unit 92 ($NHPh$) can be shown to occur according to the scheme-17 given below.

Scheme - 17



Other important and comparable ions are regarded as derived from the ion m/z 484 (see schemes 12-15).





The mass spectrum of 6-oxo-5 α -3-cholesteno[3,4]-N,N-phenylhydrazine (CCXXXV) (Fig. 7) gave molecular ion peak at $m/z\ 488\ (C_{33}H_{48}N_2O)$ followed by a strong peak at $m/z\ 487\ (M-H)$. This happens to be the base peak of the spectrum. Other important peaks were observed at $m/z\ 473\ (M-CH_3)$, $472\ (m/z\ 487-CH_3)$, $460\ (M-CO)$, $459\ (m/z\ 487-CO)$, 445 , 444 , 417 , 416 , 402 , 400 , 300 , 246 , 245 , 211 , 210 , 198 , 197 , 184 , 182 and lower mass peaks.

The phenylhydrazine (CCXXXV) being the only compound of its kind under the present study has been studied in some detail and fragmentations suggested have not been corroborated by parallel study of appropriate deuterated analogues. The whole effort at best can be summed up as an exercise in practising mass spectrometry.

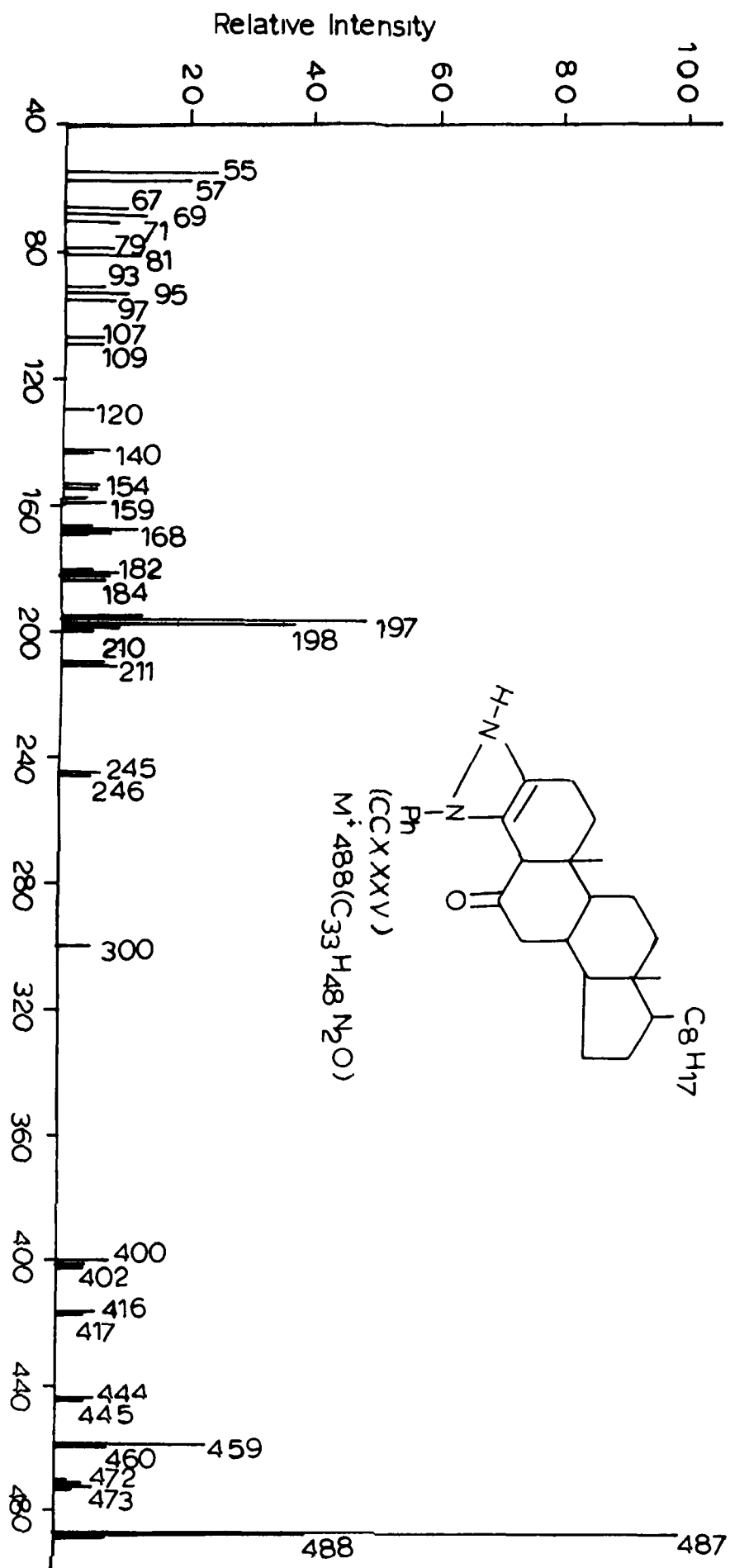
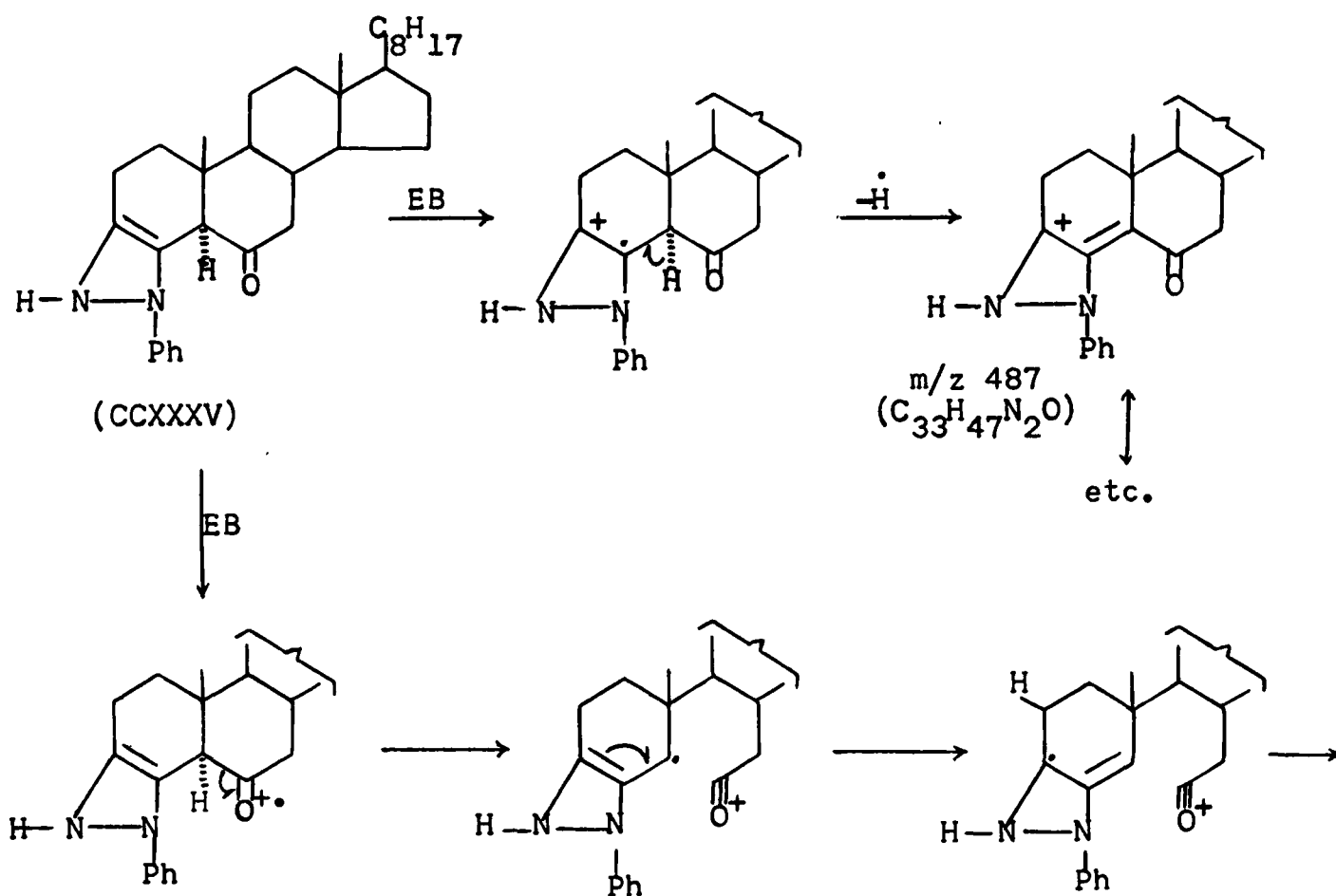


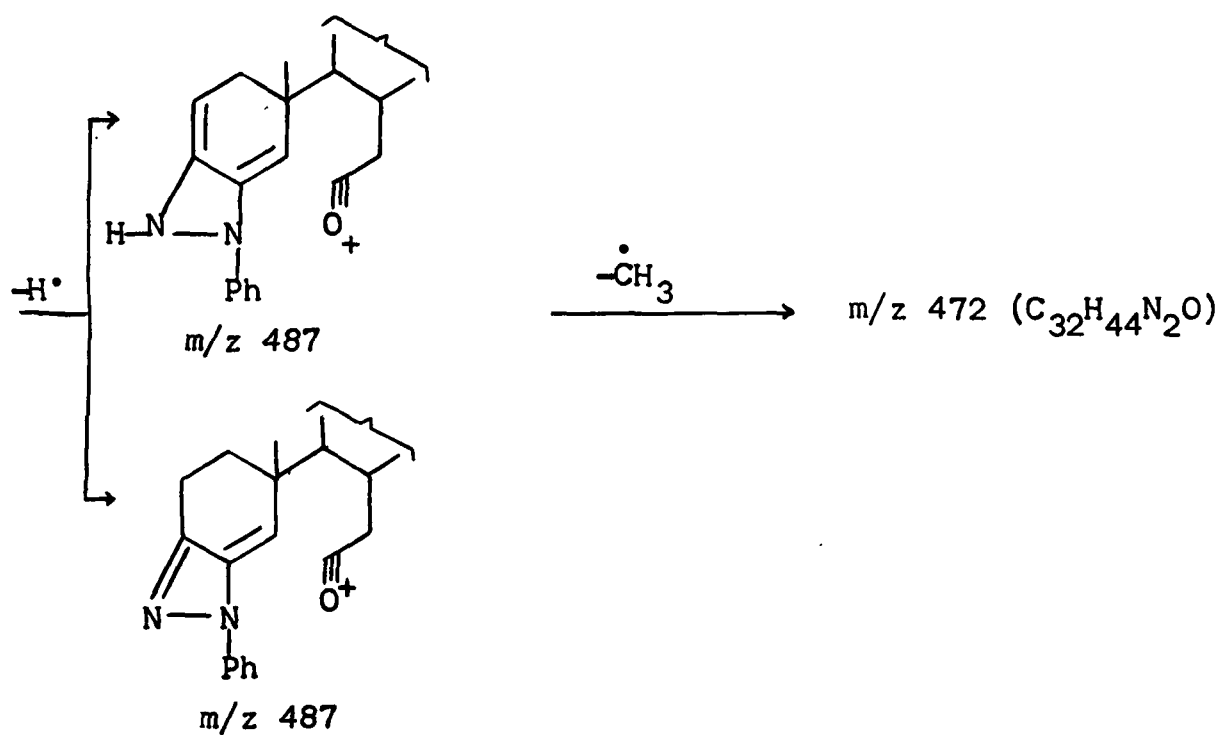
Fig. 7

m/z 487 (M-H)

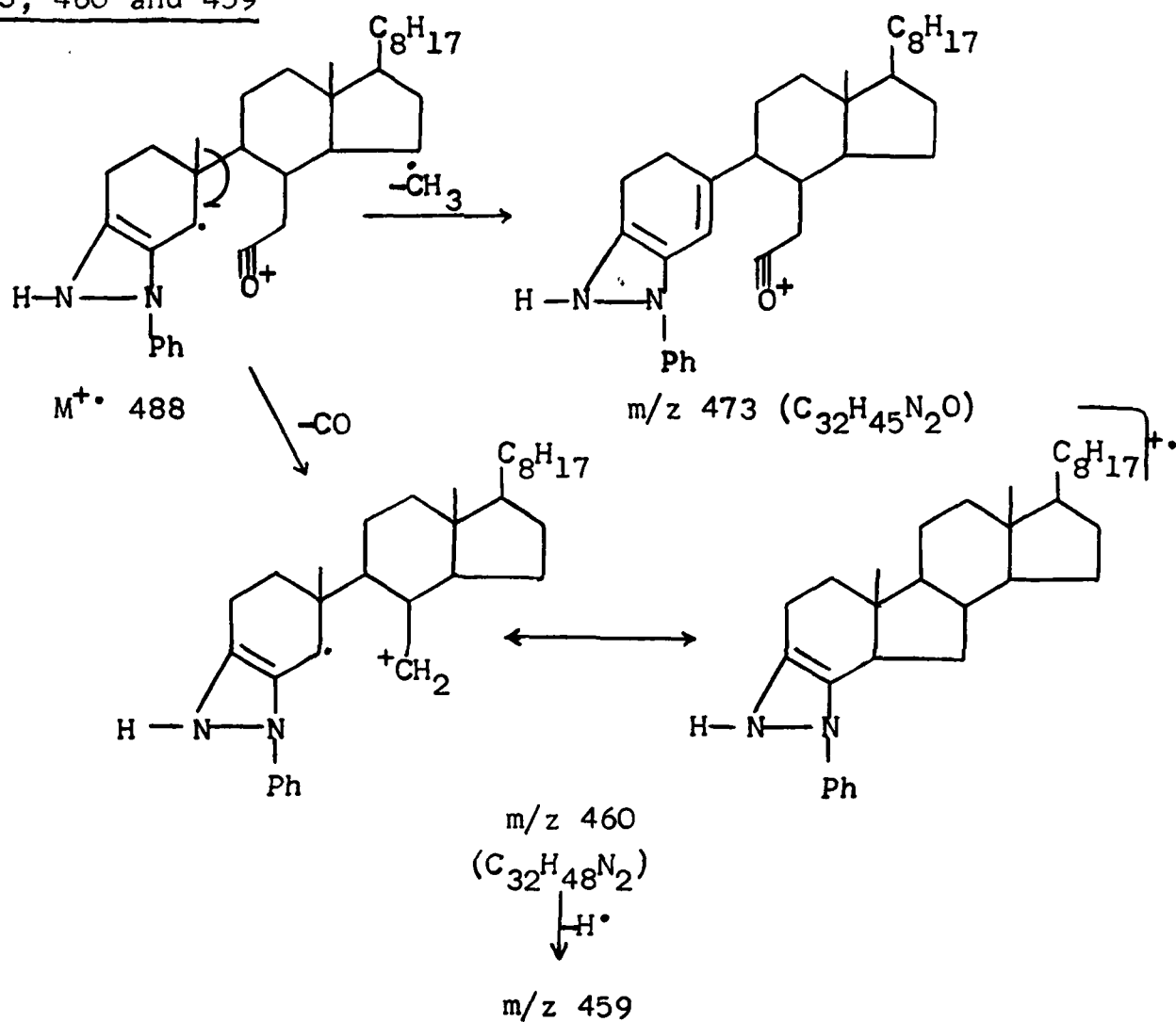
The peak at m/z 487 constitutes the base peak of the spectrum. The ion obviously arises by the loss of a hydrogen from the molecular ion. This loss can be shown to occur through different mechanisms as indicated in the given scheme-18.

Scheme - 18





$m/z\ 473, 460\ and\ 459$



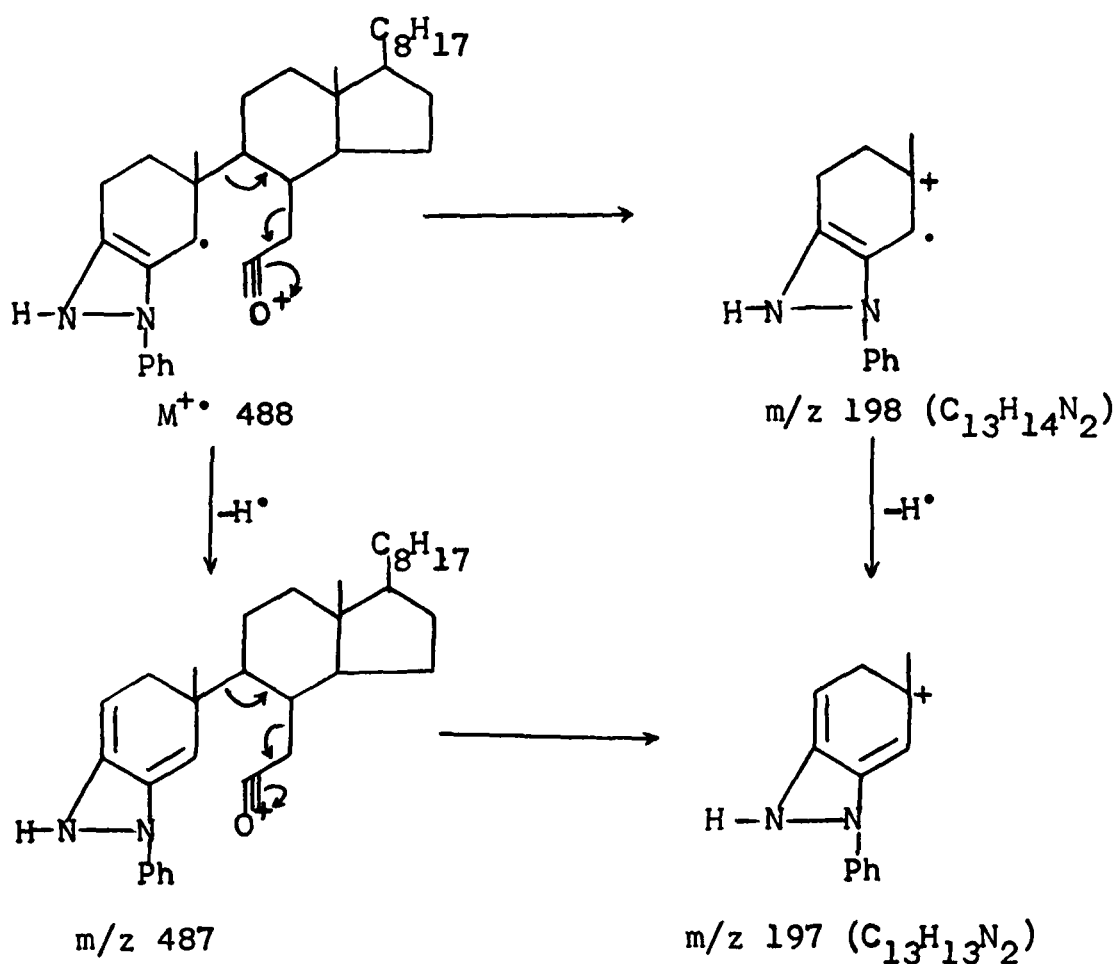
m/z 445 and 444

These ion peaks result by the loss of methyl group from m/z 460 and 459, respectively.

m/z 198 and 197

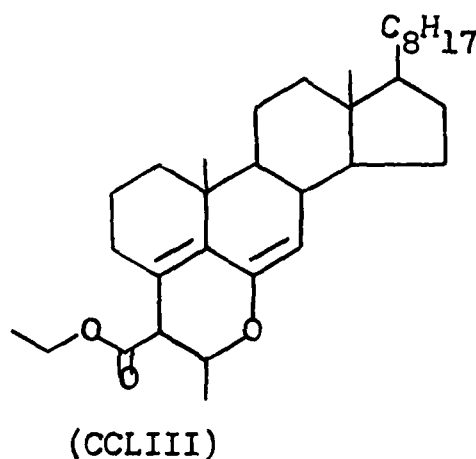
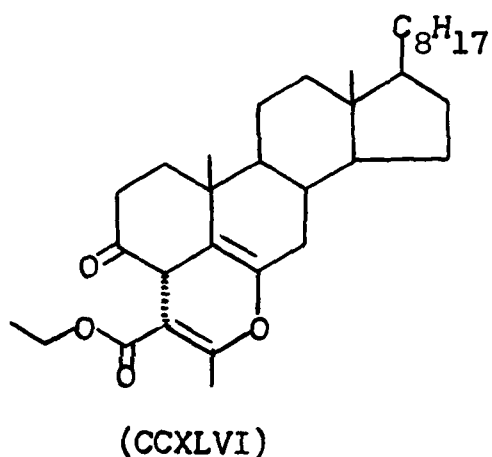
These are the two most important mid mass ion peaks in the spectrum. Their formation can be shown according to scheme-19.

Scheme - 19



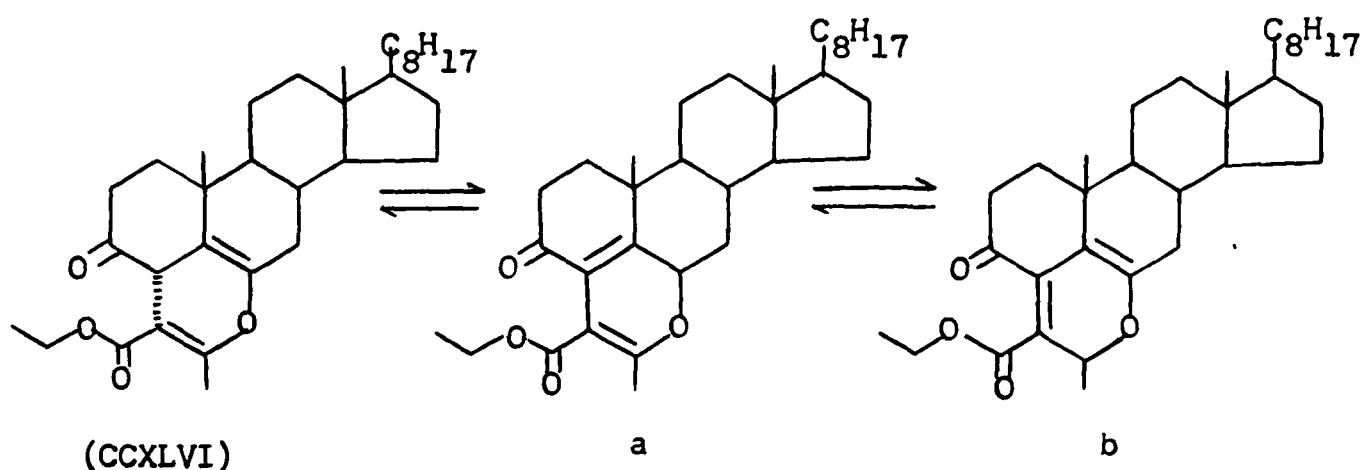
B. Steroidal pyrans - A preliminary study

A survey of the literature revealed that no mass spectral study of steroidal pyrans has been reported, though mass spectra of several pyrans have been examined^{68,71}. The present chapter, as an initial study is concerned with a very limited number of steroidal pyrans, such as 2'-methyl-3'-carboethoxy-3-oxo-5-cholesteno[4,6-de]- γ -pyran (CCXLVI) and 2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydropyran (CCLIII). Furthermore, these pyrans are not structurally very closely related to each other and therefore, their mass spectral study has very limited scope under the circumstances. Nevertheless we considered it necessary and interesting to look into the spectra of these compounds. The formation of some of the important ions has been suggested in the following schemes. These suggestions find support from the composition of the ions. However, in the absence of appropriate deuterated analogues these pathways are tentative in nature.



The mass spectrum of (CCXLVI) (Fig. 8) gave a very strong molecular ion peak at m/z 510 ($C_{33}H_{50}O_4$) followed by other relevant peaks at m/z 495 ($M-CH_3$), 466 (m/z 495- CH_2CH_3), 465 ($M-OCH_2CH_3$ or m/z 495- $CH_2=O$), 450 (m/z 495- OCH_2CH_3 or m/z 465- CH_3), 437 ($M-COOCH_2CH_3$), 422 (m/z 437- CH_3), 368 (m/z 465- $C_5H_5O_2$), 353 (m/z 368- CH_3), 180 ($C_{10}H_{12}O_3$), 135 (m/z 180-45) and lower mass peaks.

There is no $M-H$ peak in the spectrum. This observation gives credence to the proposed structure of the pyran (CCXLVI). It was suspected it could be equilibrated with the α,β -unsaturated keto structures *a* and *b* during its preparation.



The structure (CCXLVI) supported by i.r. and n.m.r. gets further support from the mass spectrum. The structure *a* was likely to show loss of hydrogen from the molecular ion whereas *b* would have shown loss of H as well as pronounced loss of a methyl group.

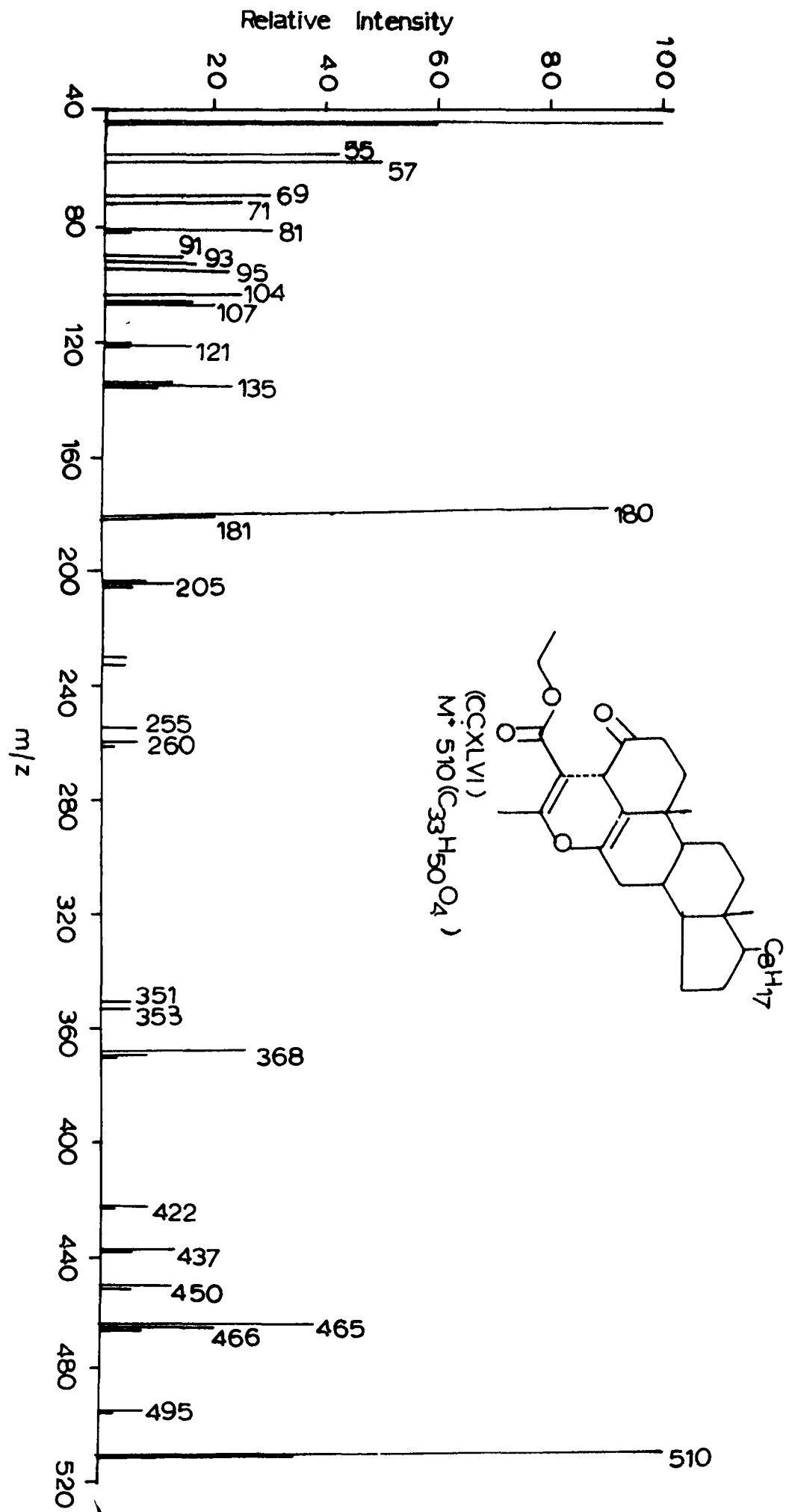
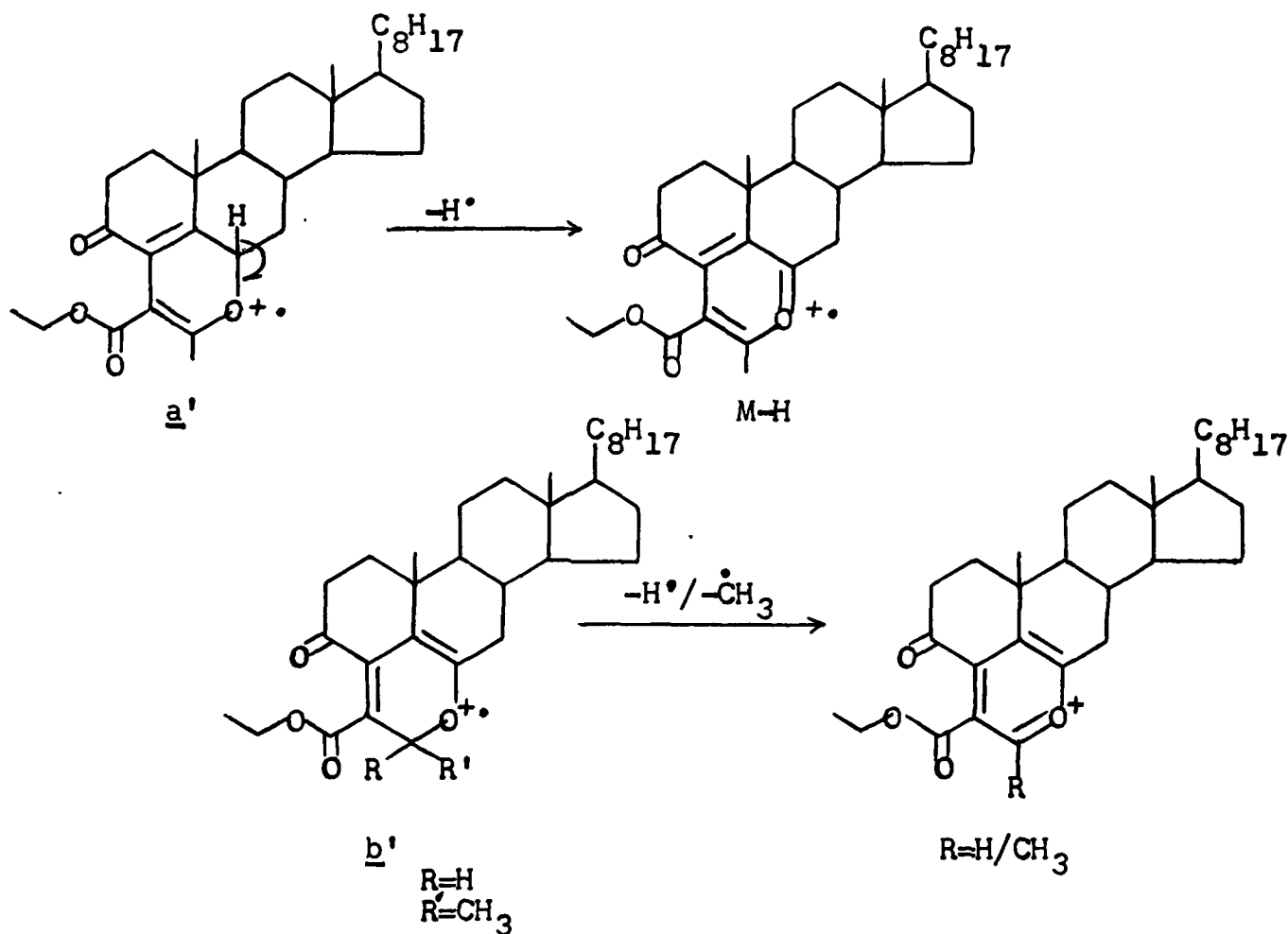


Fig. 8

Scheme - 20

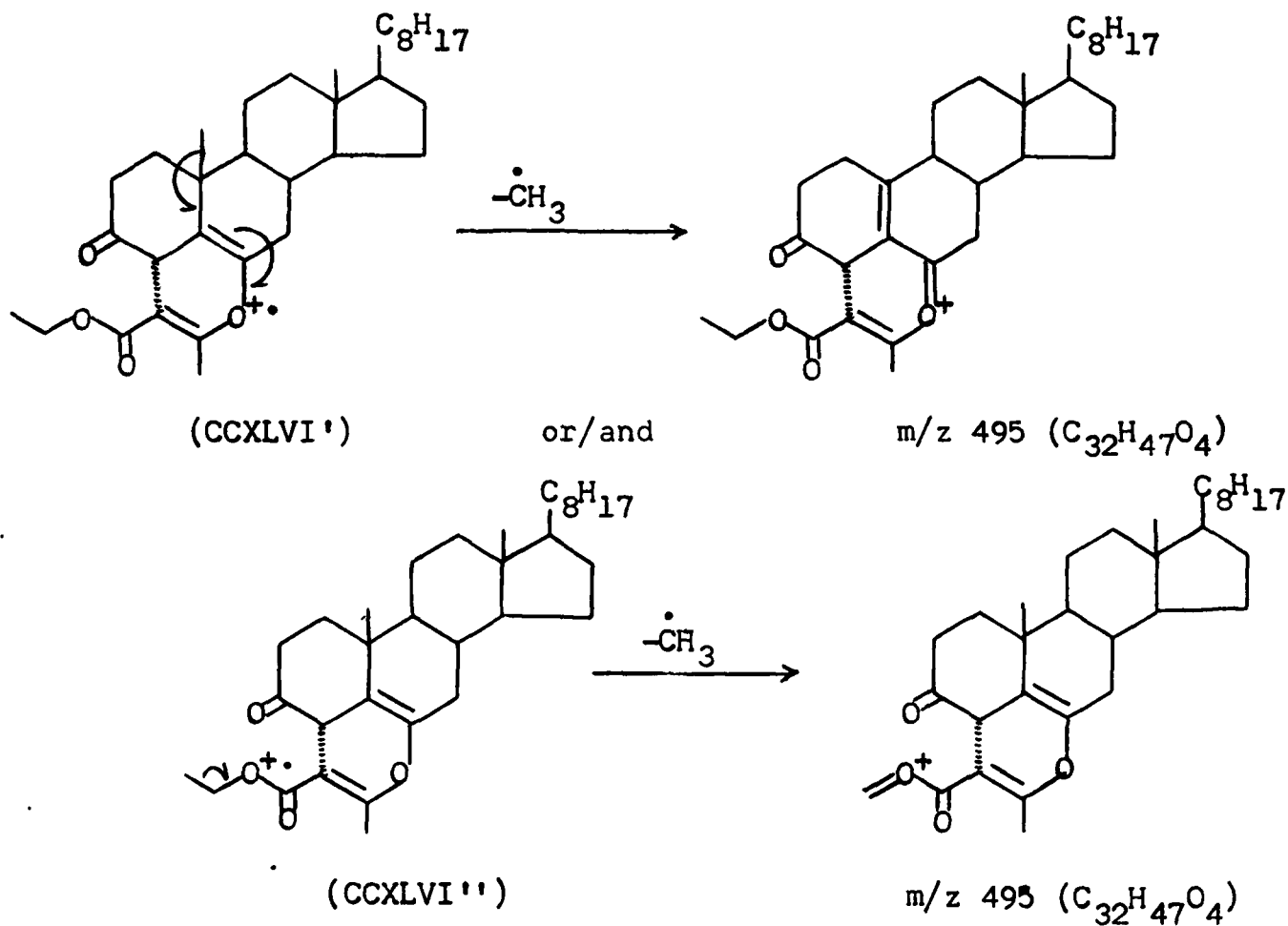


In this way the mass spectrum indirectly supported the structure (CCXLVI). It may be pointed out that the ester end in (CCXLVI) also failed to show the loss of hydrogen.

m/z 495 ($\text{M}-\text{CH}_3$)

The loss of a methyl group from the molecular ion can occur in several ways, the most preferred loss is likely to involve $\text{C}_{10}-\text{CH}_3$ as well as methyl group from the ester side chain.

Scheme - 21

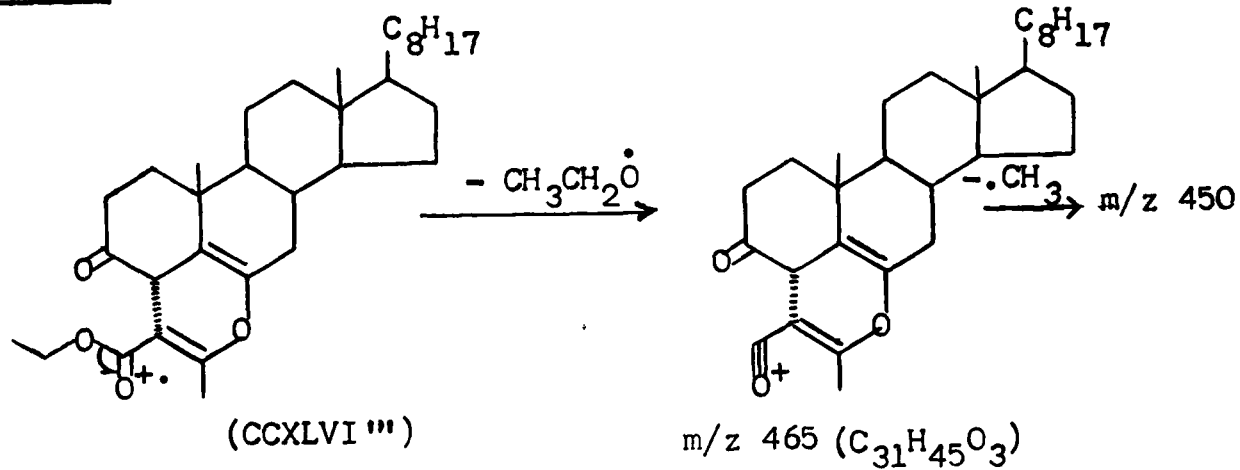
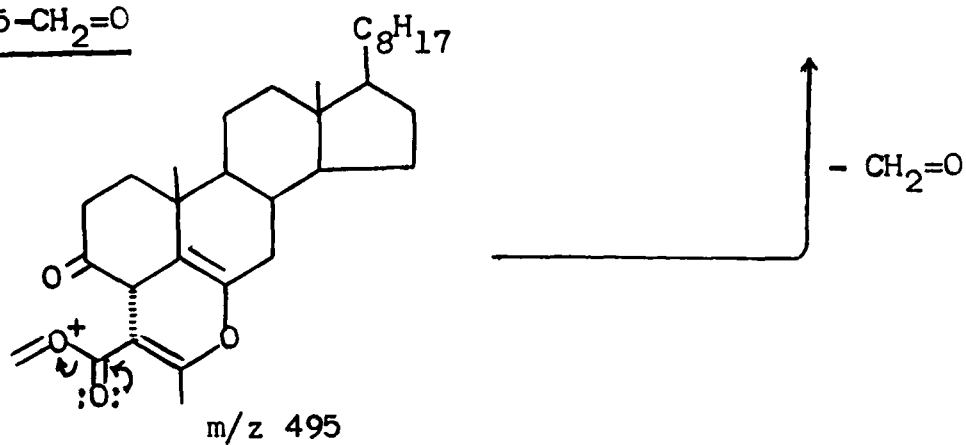
m/z 466

Apparently the ion m/z 466 results by the loss of an ethyl group from the ion m/z 495.

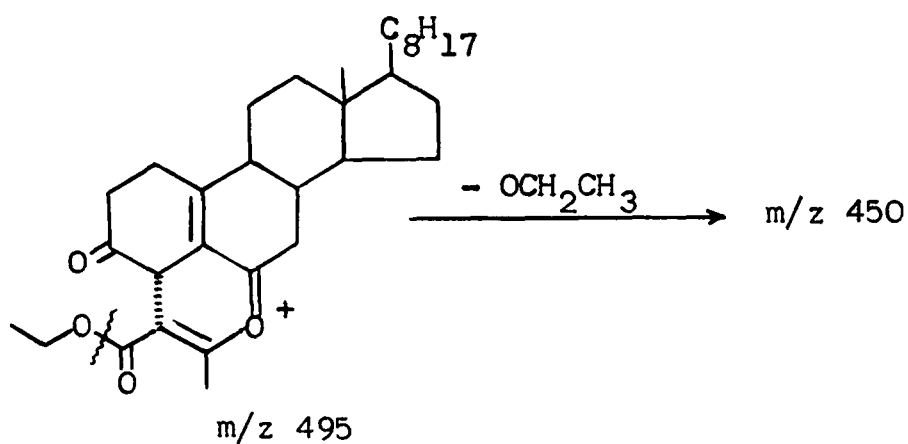
m/z 465 and 450

The ion m/z 465 is an expected and important ion. Its formation can be shown to occur in two simple ways. The subsequent loss of a methyl group will lead to ion m/z 450.

Scheme - 22

 $M^{+\bullet} - OCH_2CH_3$  $\text{m/z 495} - \text{CH}_2=\text{O}$ 

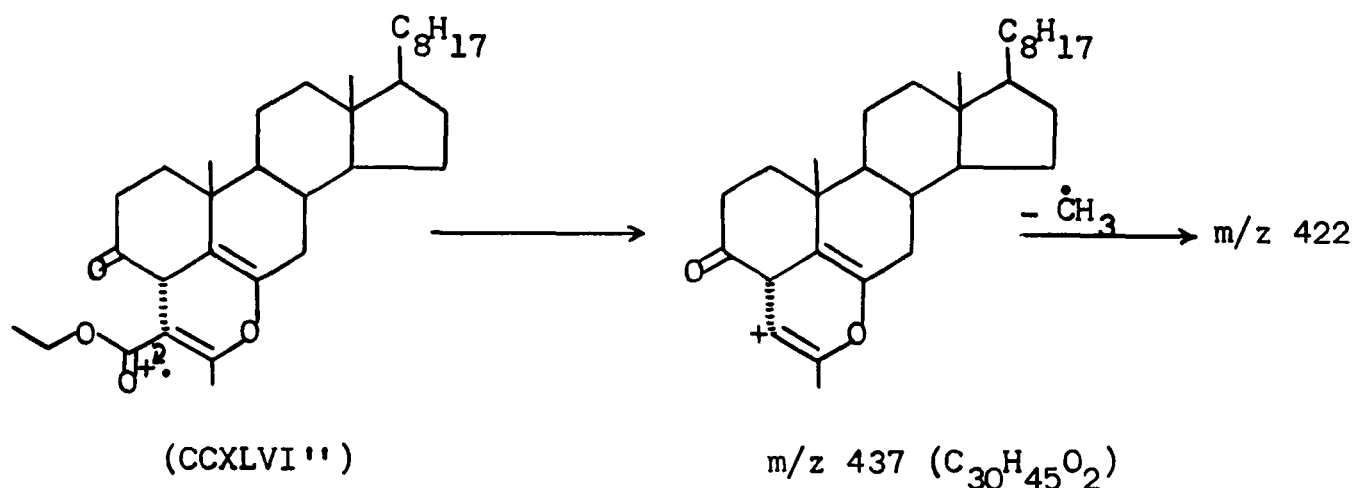
m/z 450 may also arise by the loss of OCH_2CH_3 from the ion m/z 495 .



m/z 437 and 422

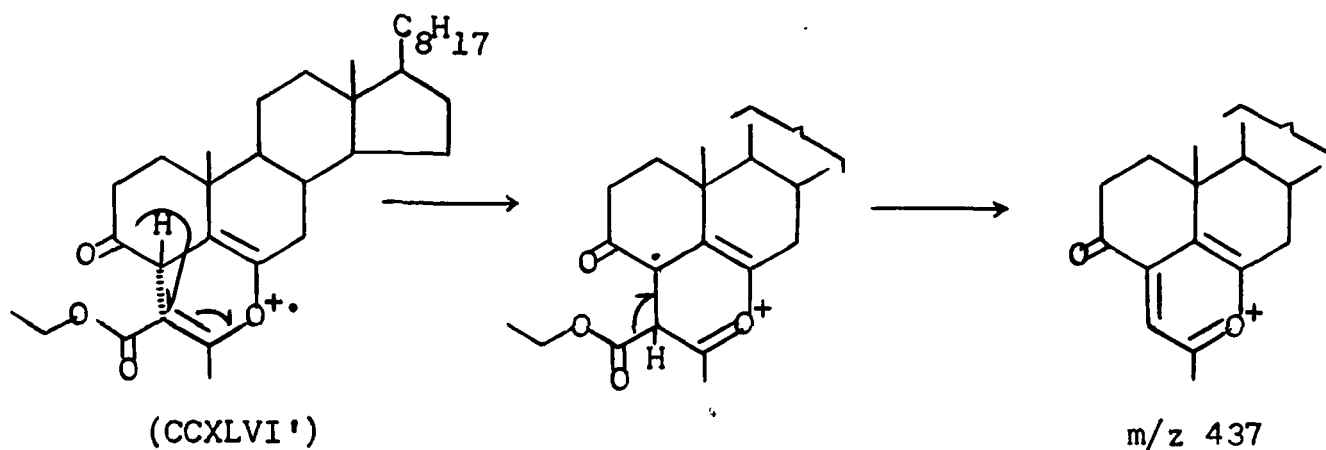
The ion m/z 437 corresponds to the loss of mass unit 73 from the molecular ion. This loss involves the pyran side chain of $\text{COOCH}_2\text{CH}_3$, not a very favourable situation in the present case in the sense that the cleavage of a vinylic bond is involved.

Scheme - 23



Alternatively the genesis of the ion m/z 437 can be shown according to scheme-24. This pathway avoids the cleavage of a vinylic bond.

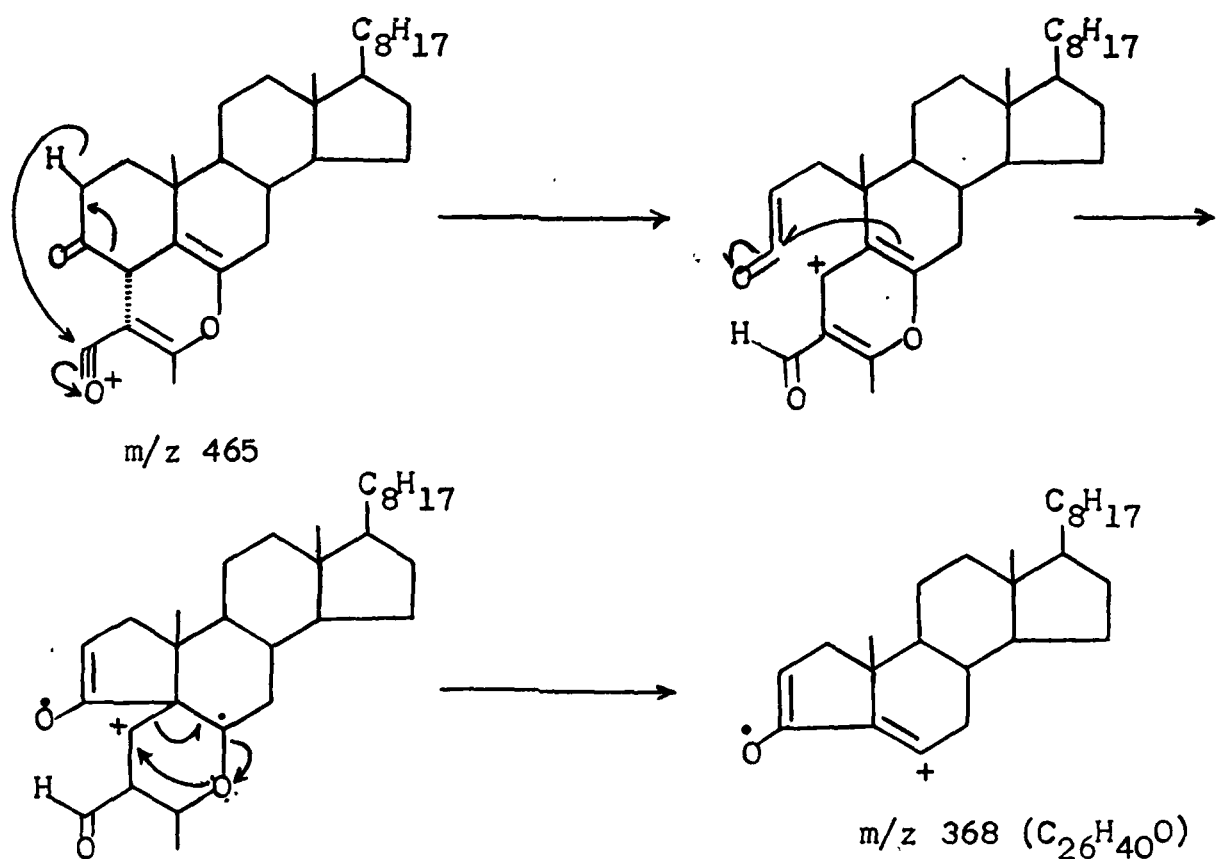
Scheme - 24



m/z 368

The ion m/z 368, with its significant relative abundance, can be shown to arise from the ion m/z 465 involving a series of not so simple cleavages.

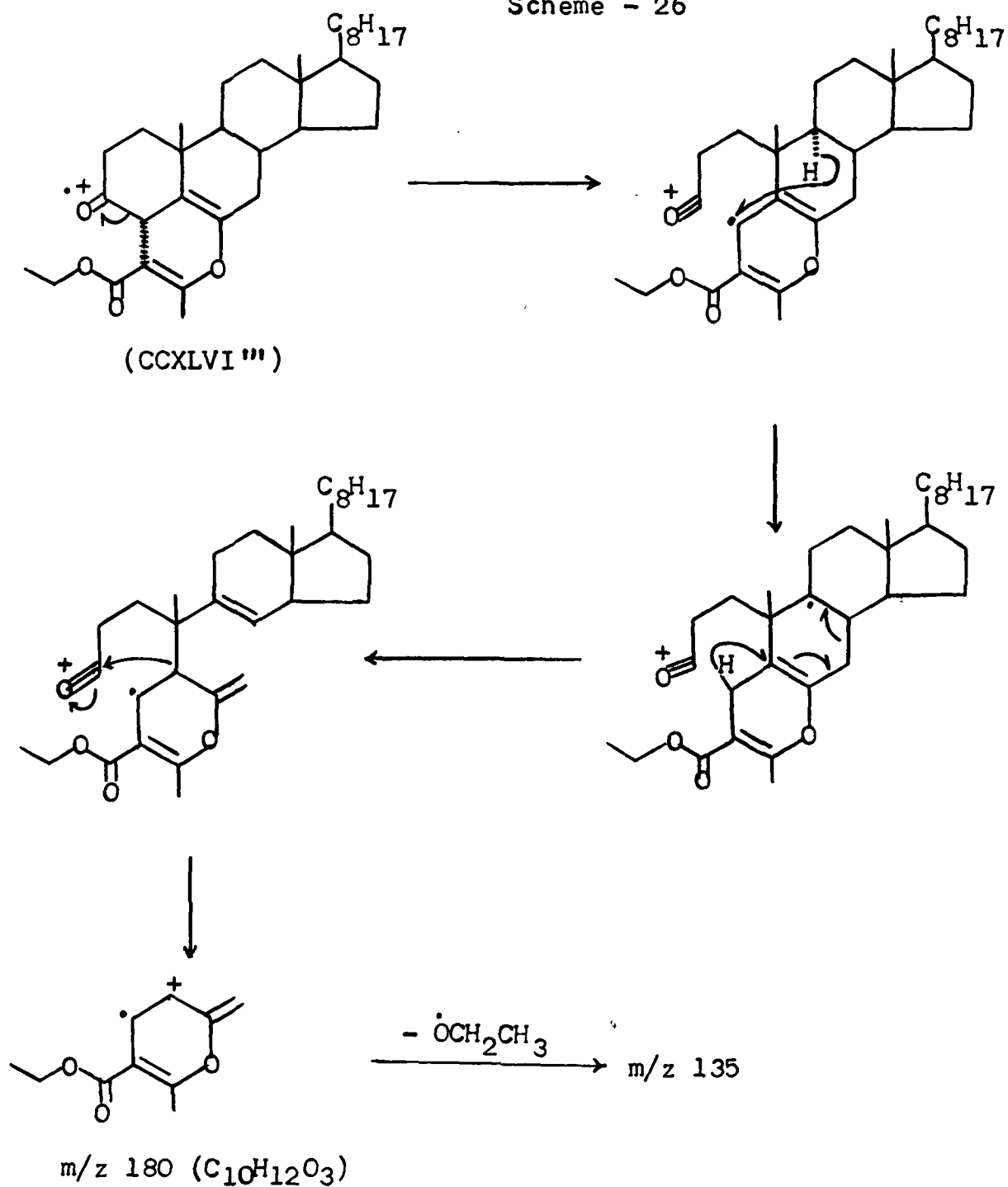
Scheme - 25

m/z 180

The ion peak at m/z 180 is nearly as strong as the base peak. Its composition ($C_{10}H_{12}O_3$) suggests that it may be mainly

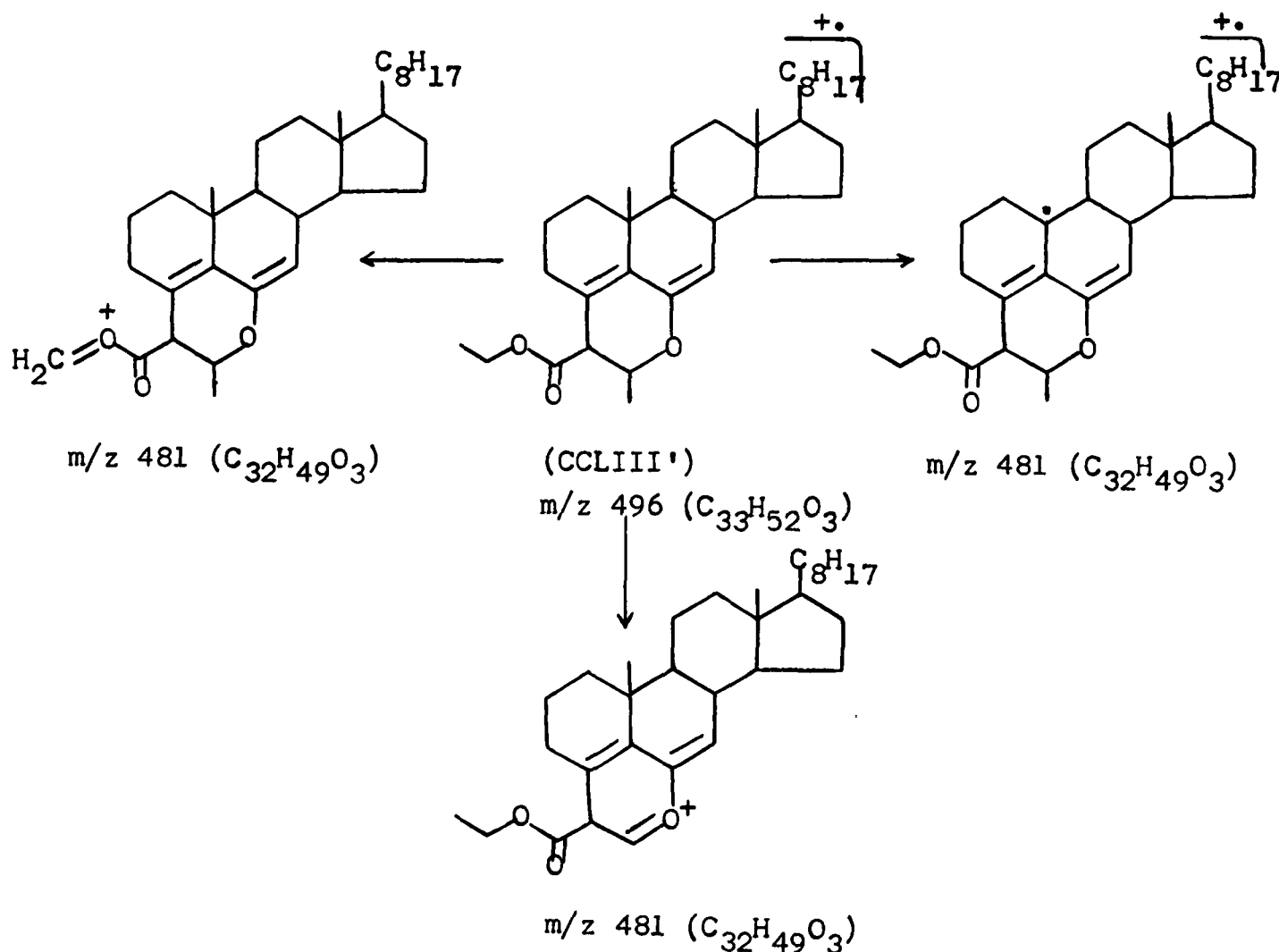
composed of the pyran moiety of the molecule. The formation of the ion m/z 180 involves a series of cleavages and an attempt has been made to rationalize its formation in scheme-26.

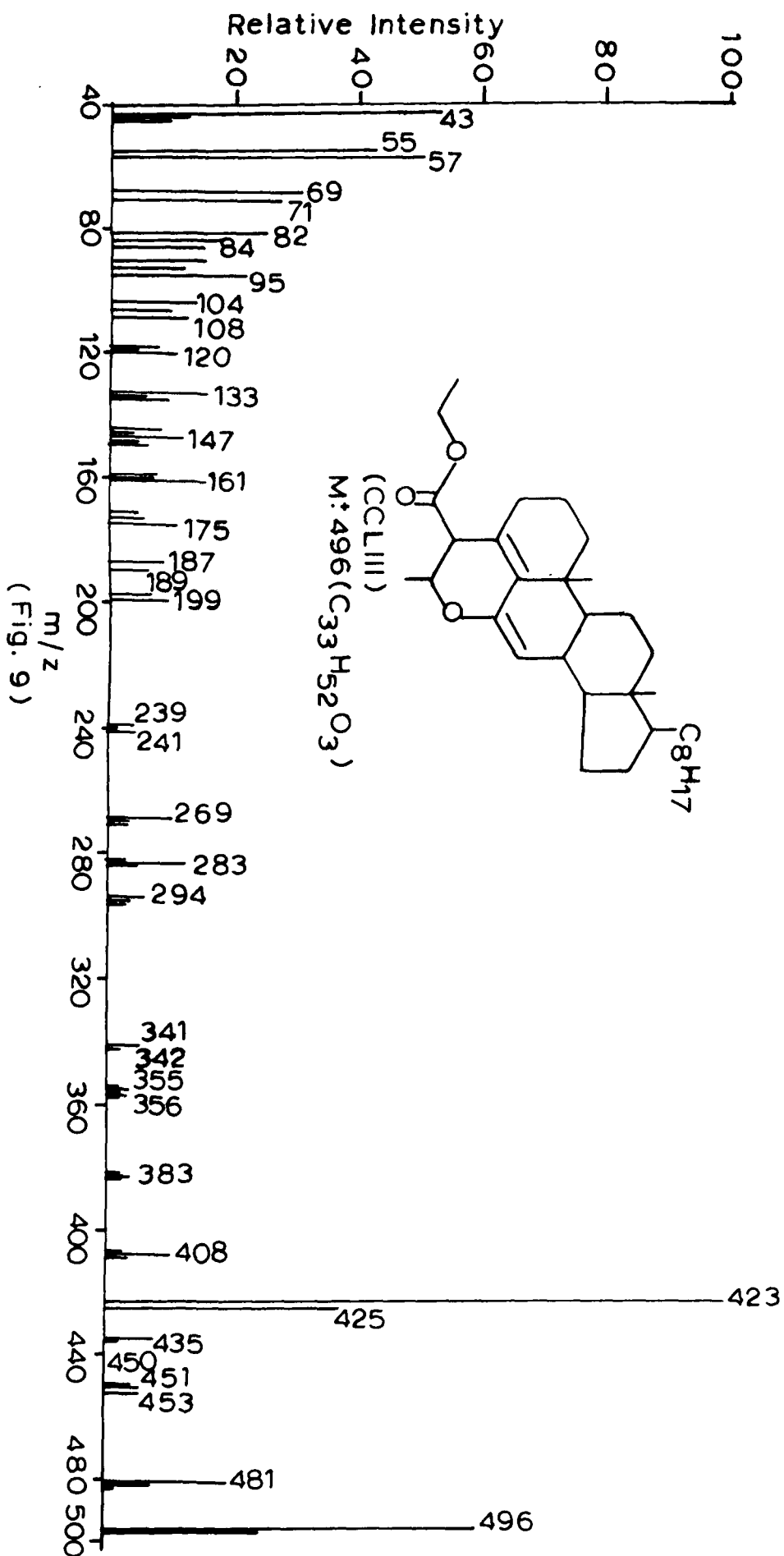
Scheme - 26



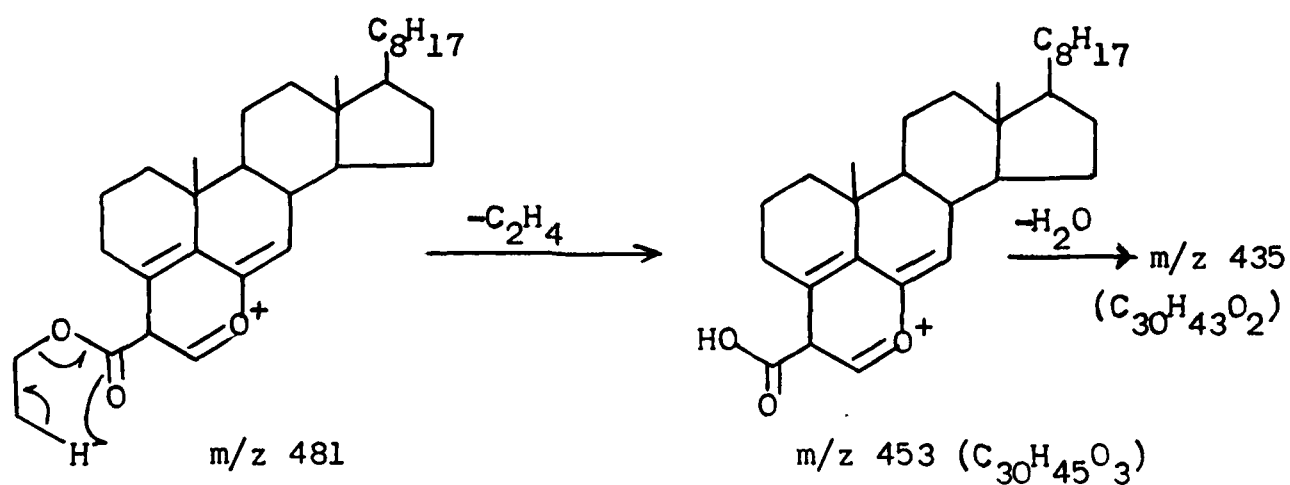
The mass spectrum of 2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydropyran (CCLIII) (Fig. 9) gave molecular ion peak at m/z 496 ($C_{33}H_{52}O_3$) along with other significant ion peaks at m/z 481 ($M-CH_3$), 453 (m/z 481- C_2H_4), 451 ($M-OC_2H_5$), 450, 435, 423 (base peak; $M-73$), 408, 383, 356, 355, 342, 341, 294, 283, 269, 189, 175 and lower mass peaks.

m/z 481 ($M-CH_3$)

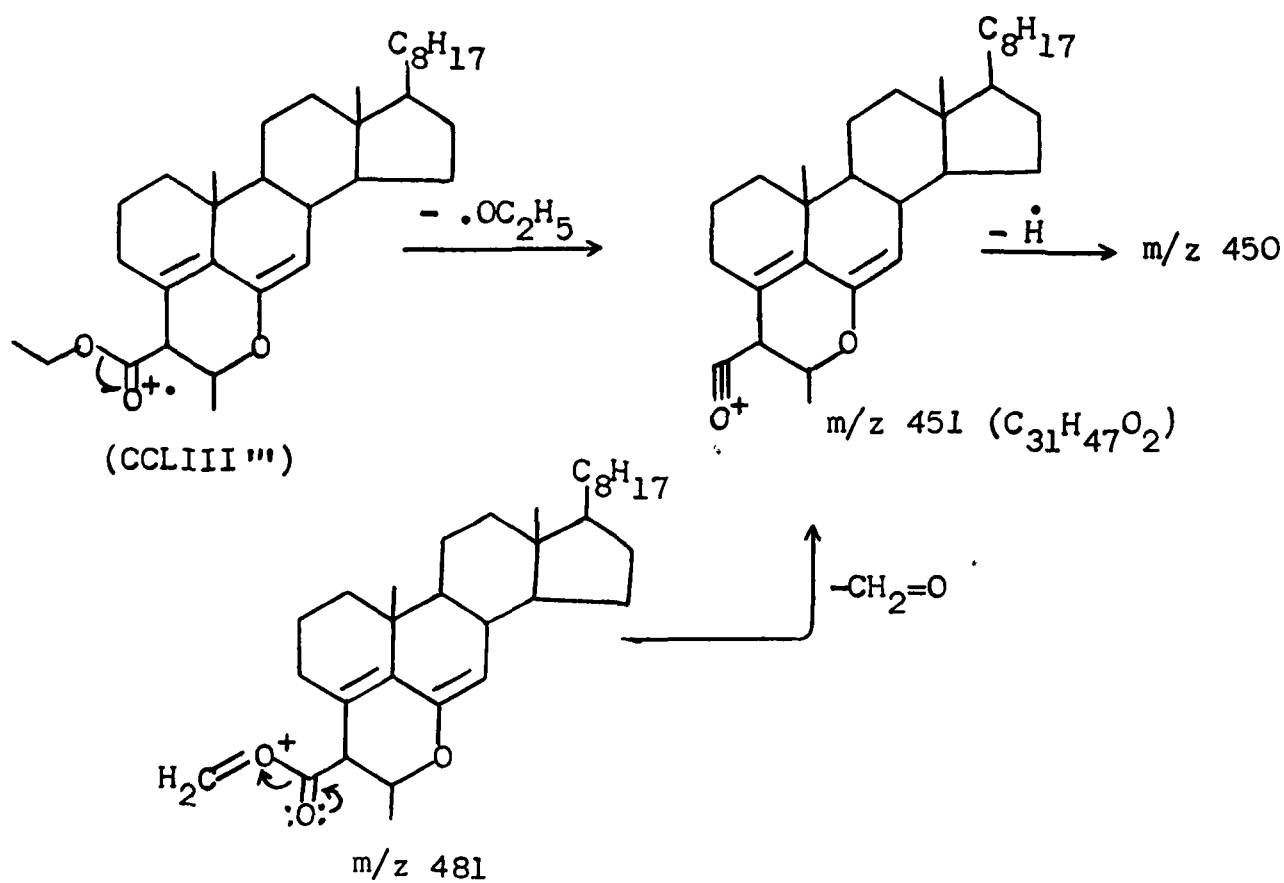




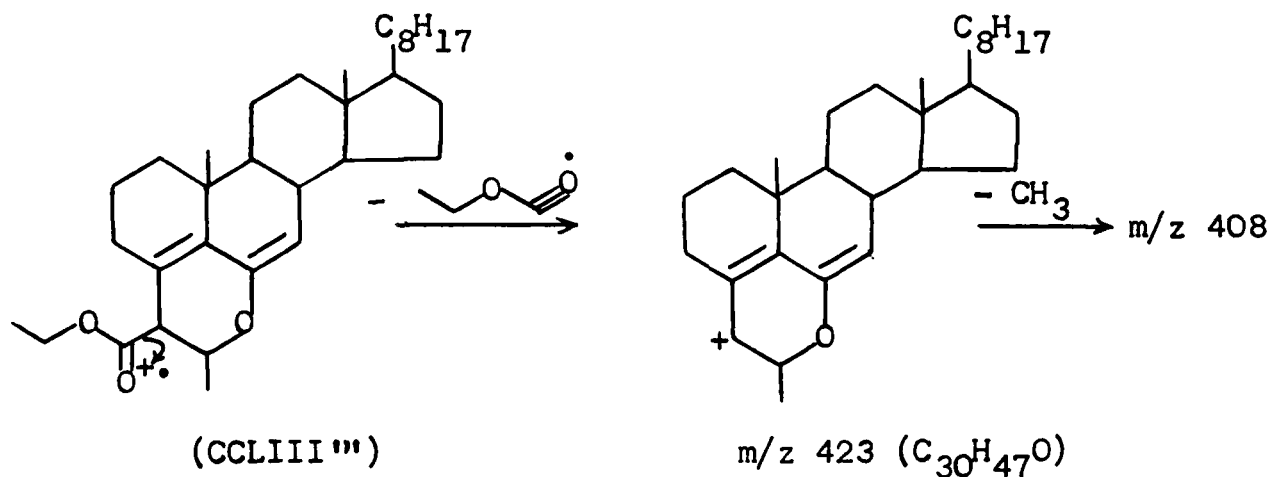
m/z 453 (m/z 481 - C₂H₄) and 435



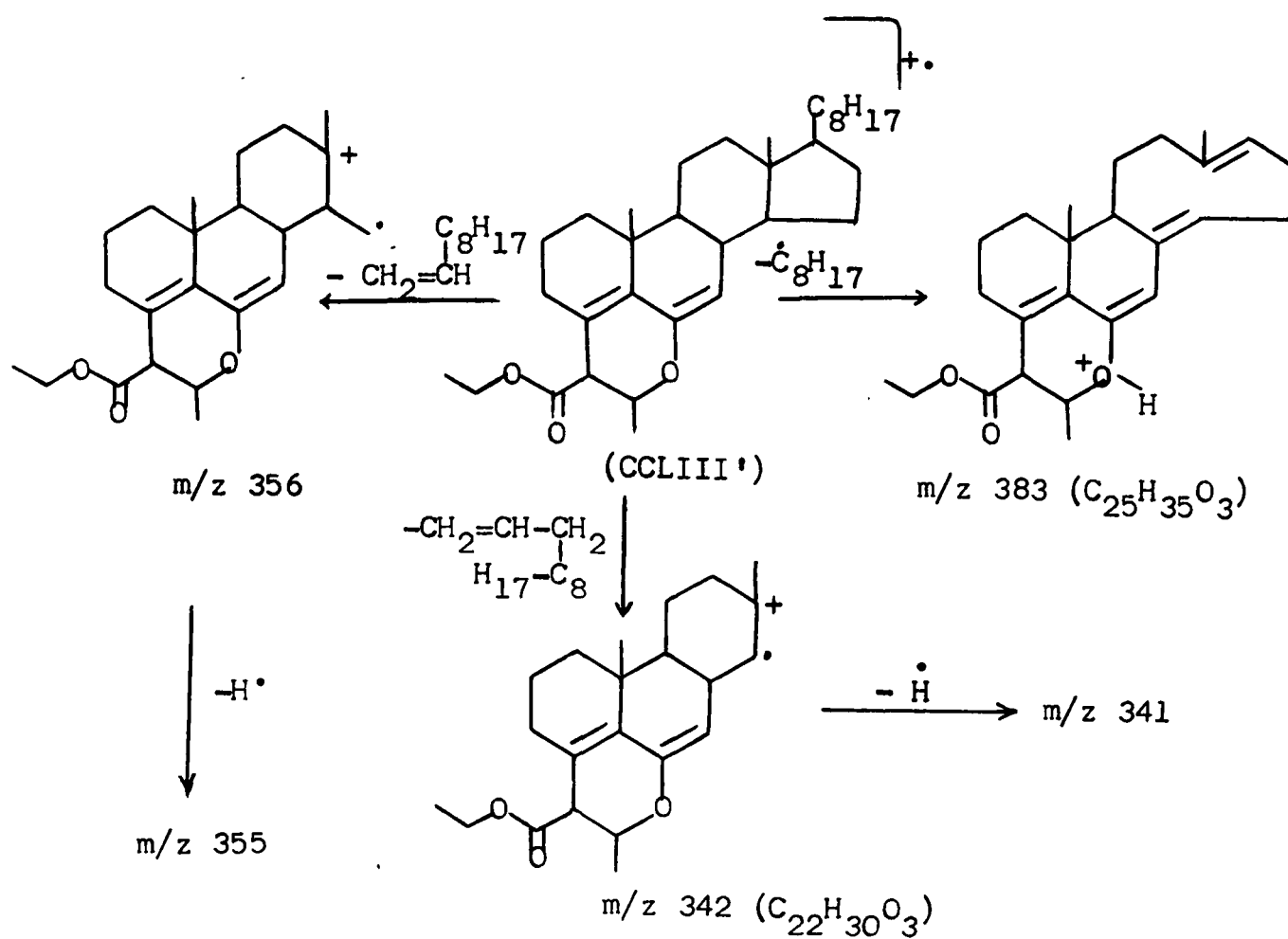
m/z 451 (M - OC₂H₅) and 450



m/z 423 (base peak, M-OCOC₂H₅) and 408

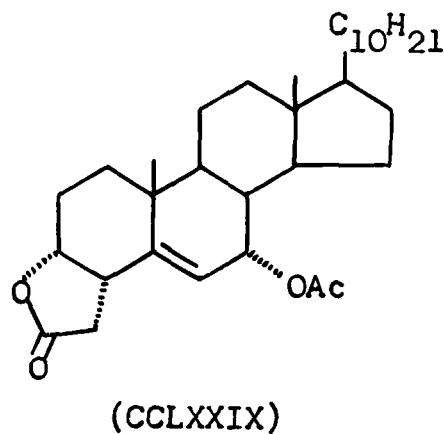
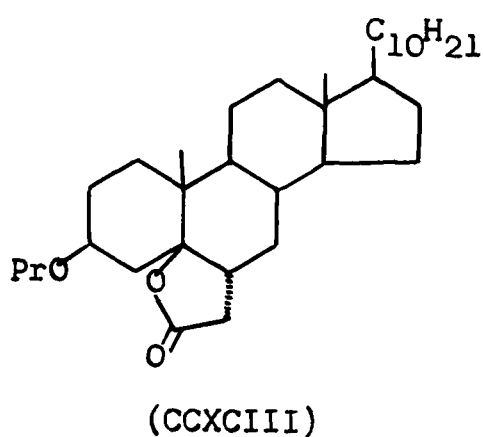


m/z 383, 356, 355, 342 and 341

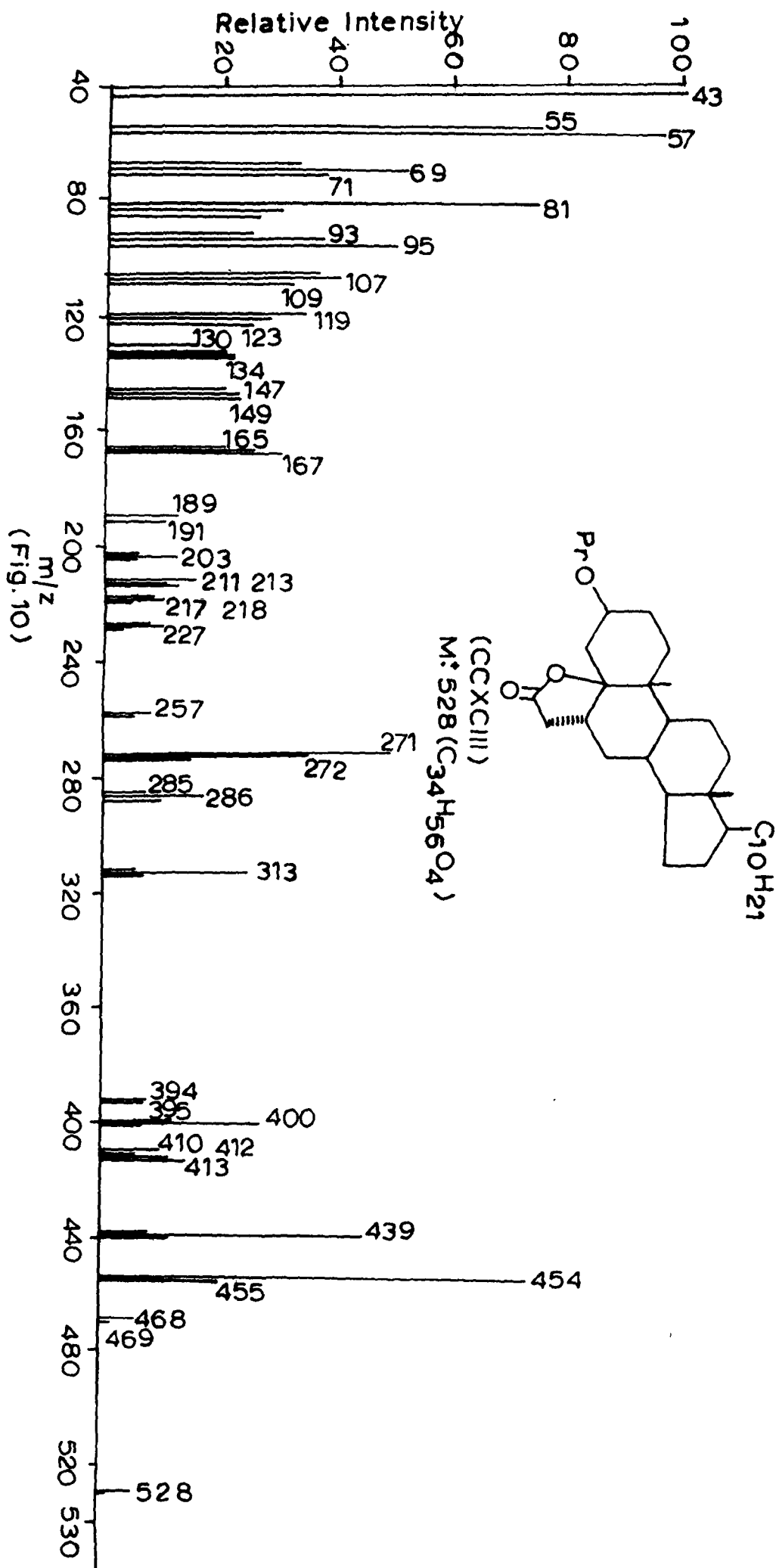


C. Steroidal γ -lactones

The concluding part of the chapter deals with the mass spectral study of two γ -lactones belonging to the stigmastane series. They are 3β -propionyloxy- 5β -hydroxystigmastan- 6α -yl acetic acid γ -lactone (CCXCIII) and 7α -acetoxy- 3α -hydroxystigmastan- 5 -en- 4α -yl acetic acid γ -lactone (CCLXXIX). In an earlier work mass spectra of several γ -lactones belonging to the cholestane series have been examined¹²⁶. It may be pointed out that the main idea at present is to compare the spectra of the γ -lactones in the two series, namely the cholestane and the stigmastane series.



The mass spectrum of (CCXCIII) (Fig. 10) gave molecular ion peak at m/z 528 ($C_{34}H_{56}O_4$) followed by other ion peaks m/z 469, 468, 454 ($M-CH_3CH_2COOH$) or (469-15), 439 (m/z 454-15), 413, 412 (m/z 454- $CH_2=C=O$), 410 (m/z 454- CO_2), 400 (m/z 454- $CH_2=CH-CH=CH_2$), 395 (m/z 454-59 or 410- CH_3), 394 (454-60 or 410-15+H), 313 (m/z 454- $C_{10}H_{21}$), 286 (m/z 454-168), 285, 272 (m/z 454-172), 271,

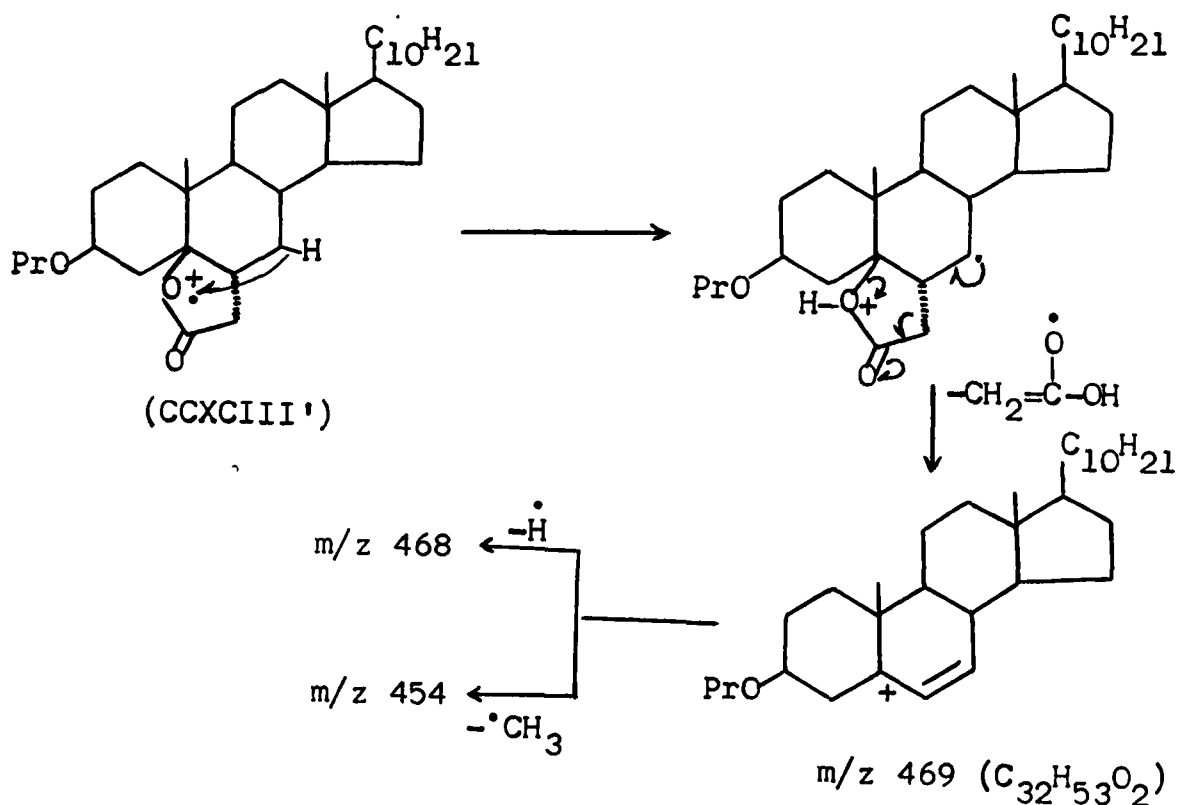


257 (m/z 272-15), 227 (m/z 271- CO_2), 218 (m/z 272- C_4H_6), 217, 213 and lower mass peaks.

m/z 469 ($\text{M}-\text{CH}_2\text{COOH}$)

The ion m/z 469 results by the loss of mass unit 59 (CH_2COOH) from the molecular ion. This break down may involve one of the hydrogen atoms from C_1 , C_7 or C_8 migrating to the lactone ether oxygen (1,6-cyclic transition state). For no particular reason other than mechanistic consideration, one of the C_7 -hydrogen atoms has been shown to take part in the fragmentation process (scheme-27).

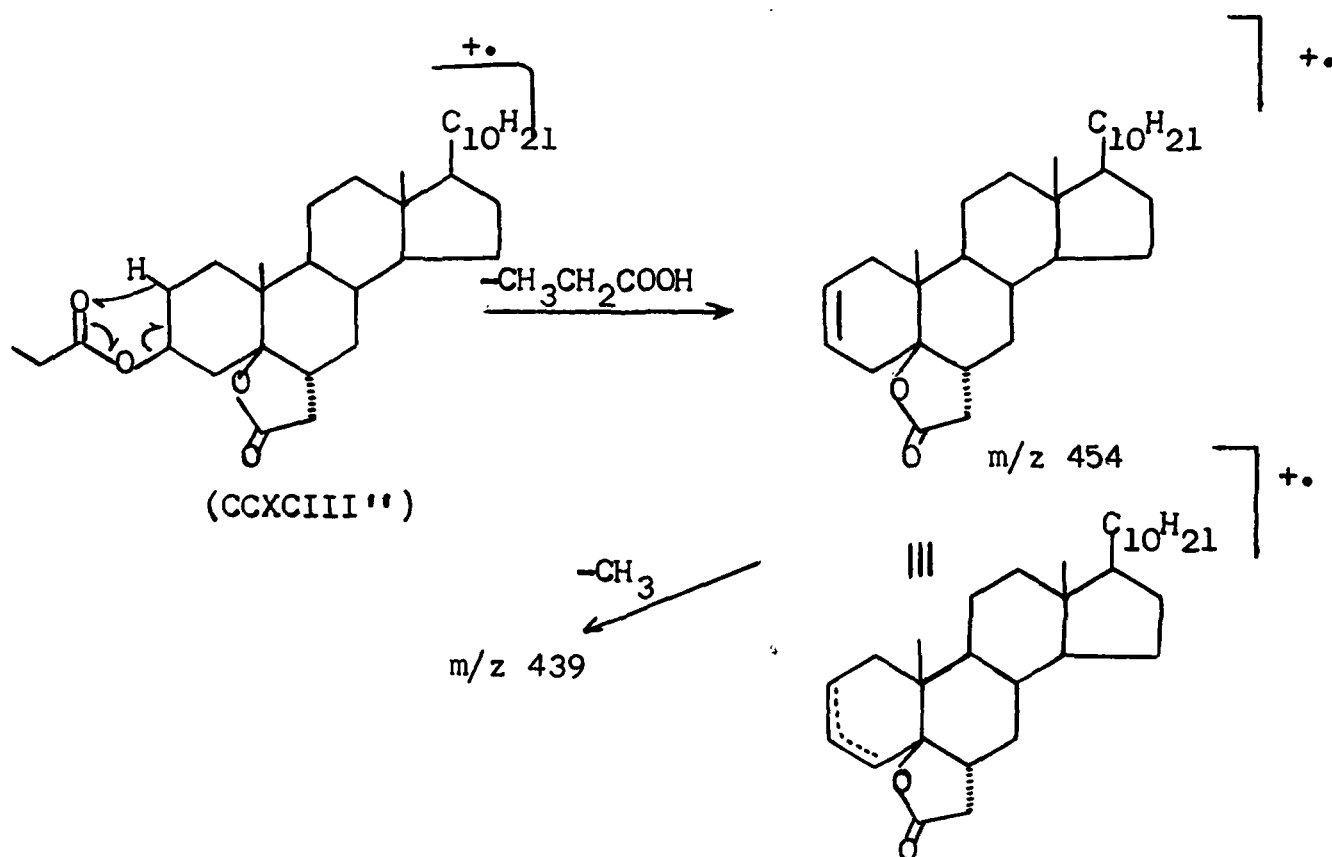
Scheme - 27



m/z 454 ($C_{31}H_{50}O_2$) and 439

($M-CH_3CH_2COOH$ or $m/z\ 469-CH_3$)

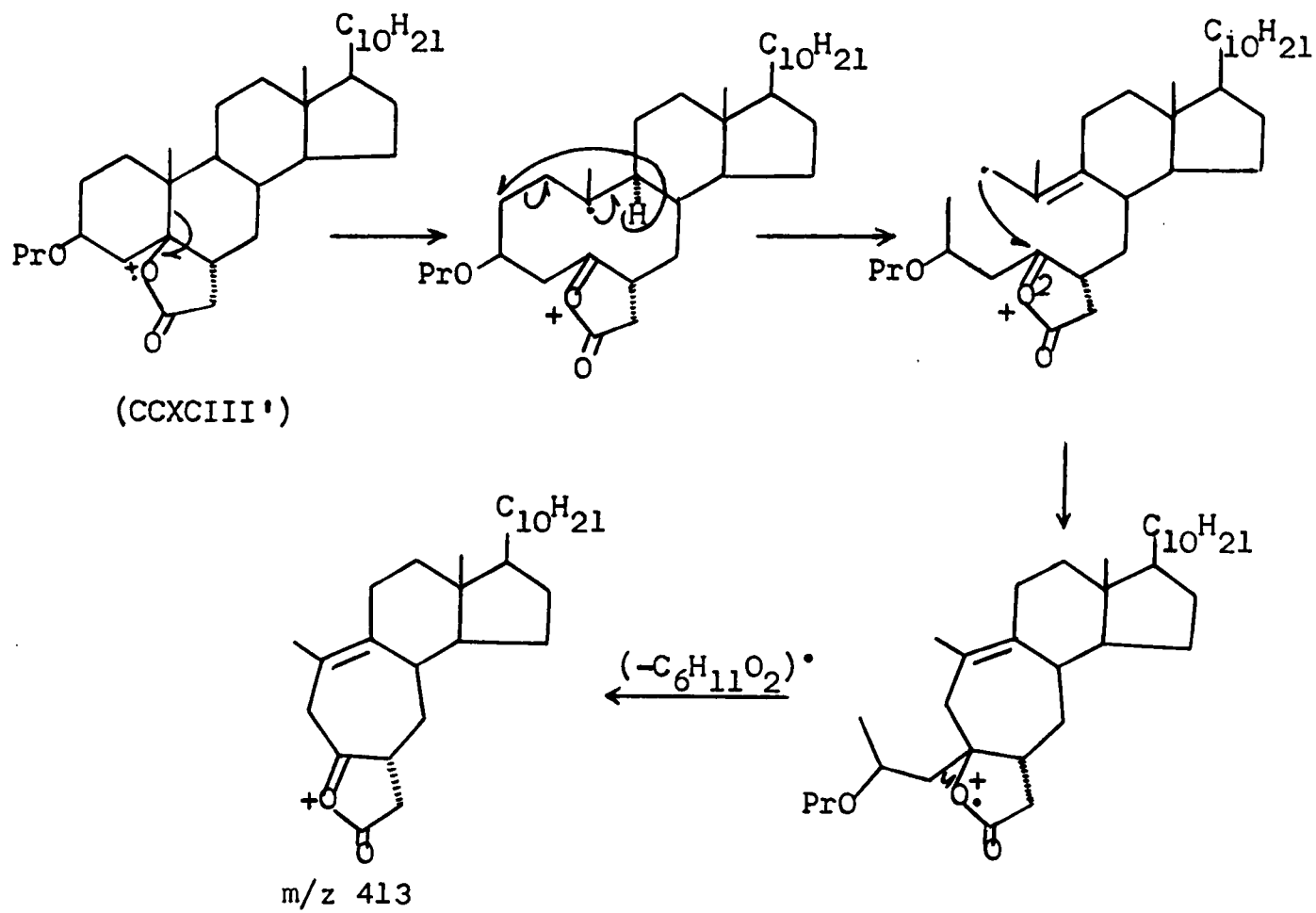
Scheme - 28



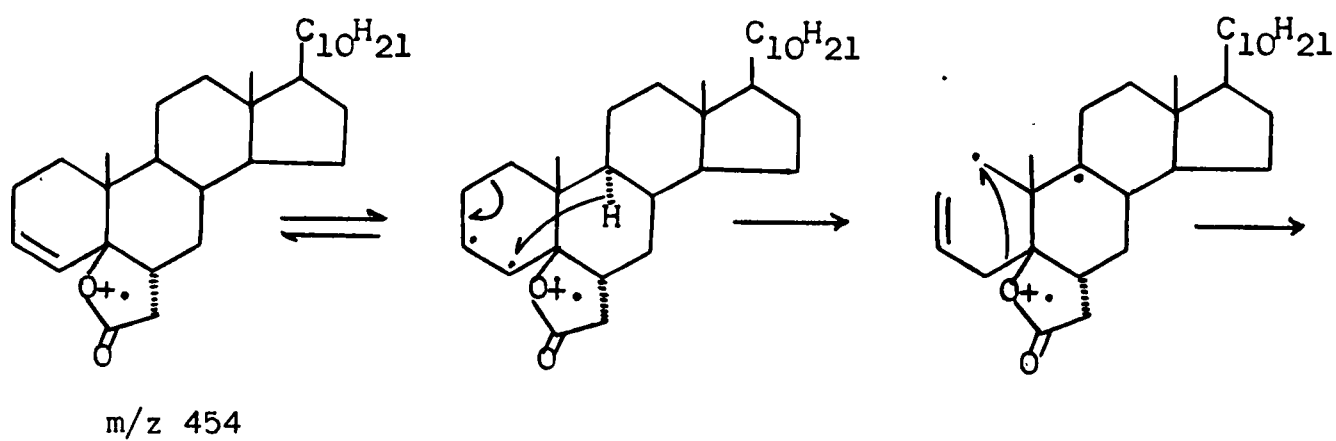
m/z 413 ($C_{28}H_{45}O_2$)

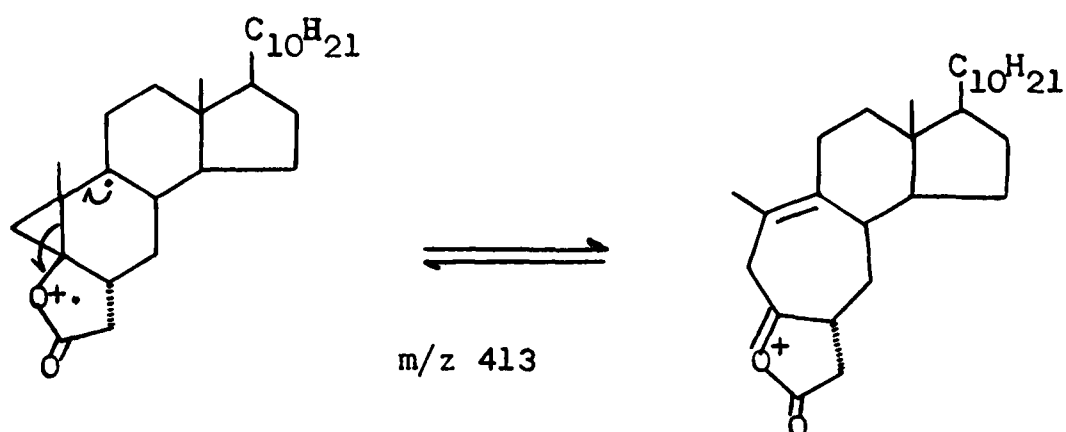
The ion with the composition $C_{28}H_{45}O_2$ implies either the loss of $CH_3CH_2COOCHCH_2$ from the molecular ion or the loss of $CH_2=CH-\dot{C}H_2$ (mass unit 41) from the ion $m/z\ 454$. Both the possibilities apparently involve complex fragmentation process and these have been considered in schemes 29 and 30 respectively.

Scheme - 29



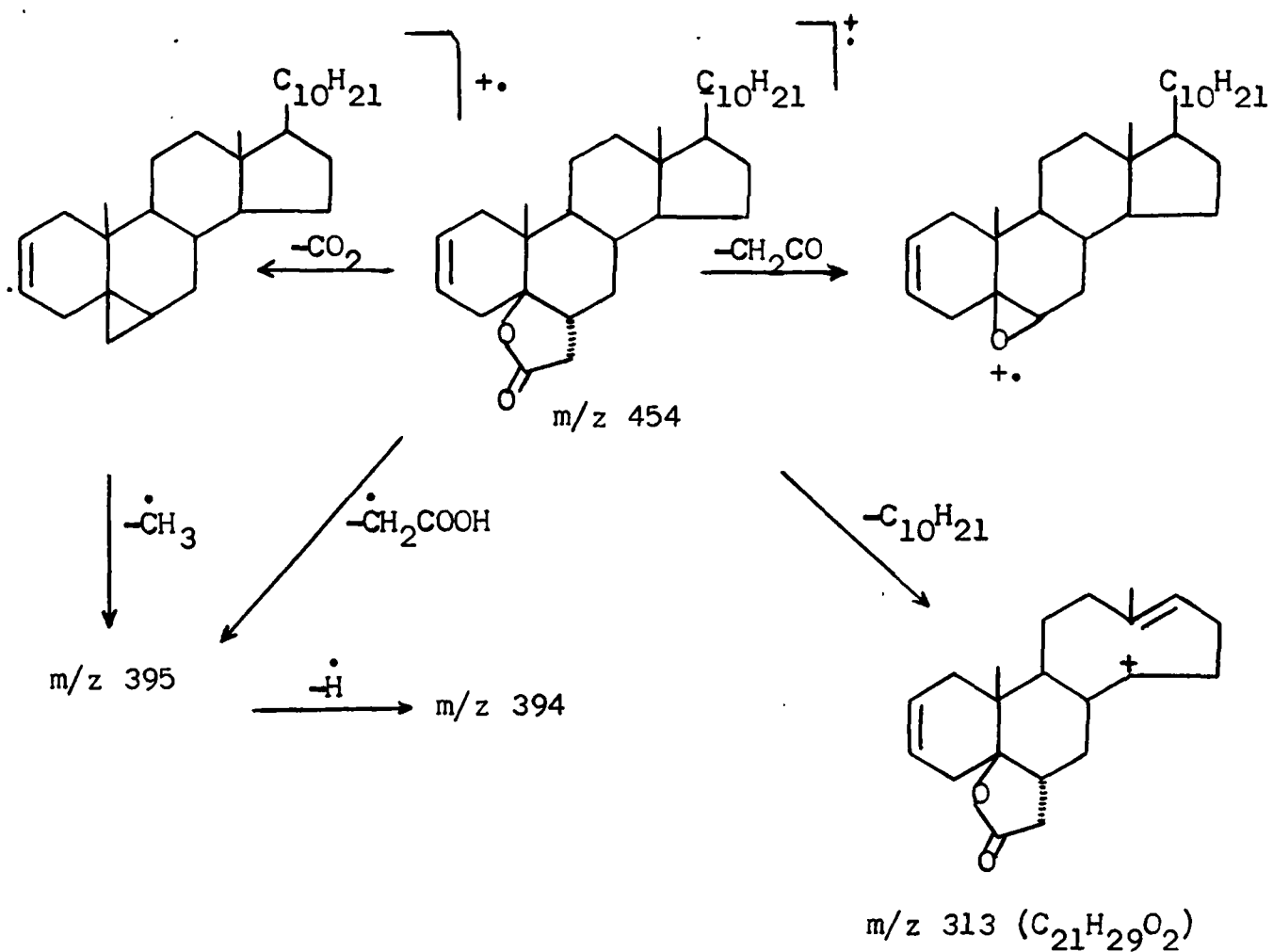
Scheme - 30

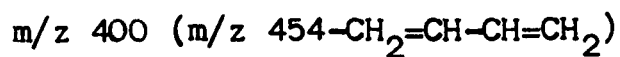
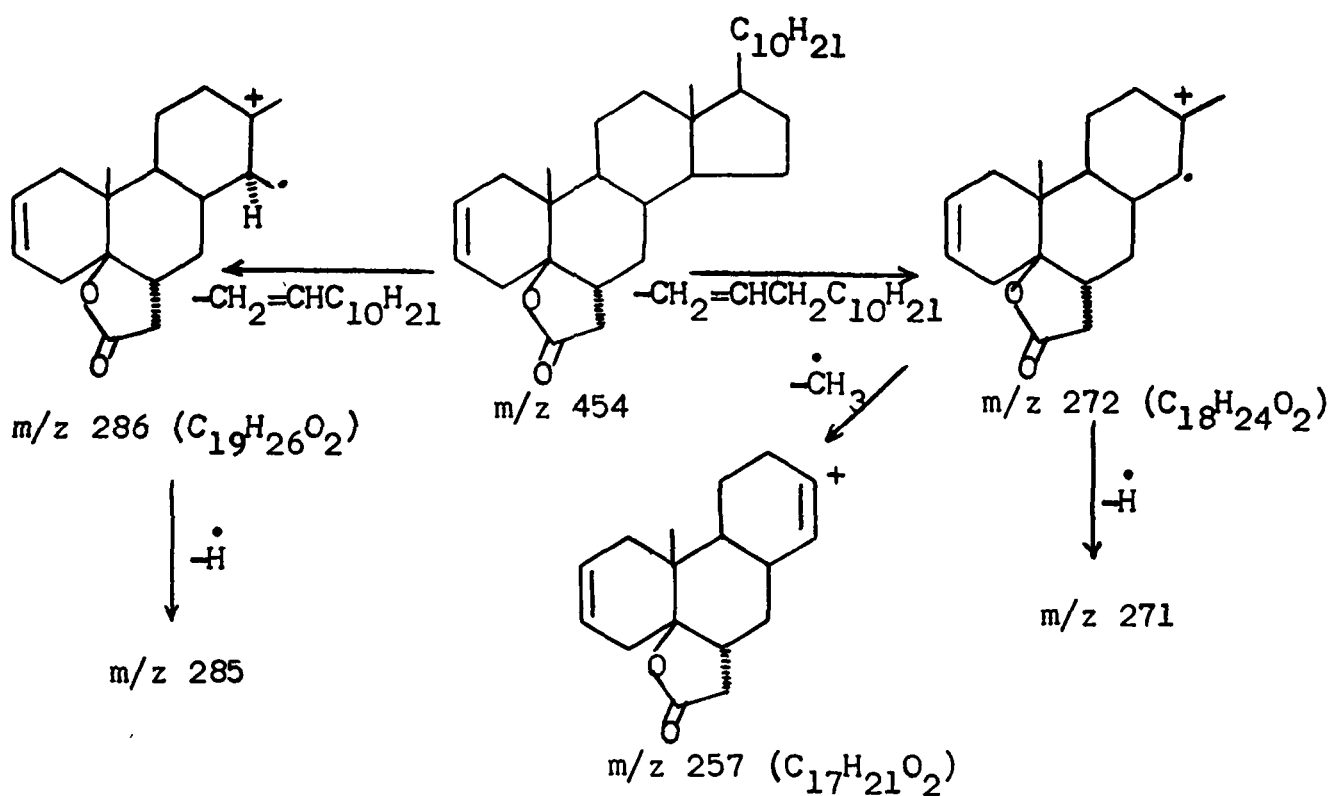




m/z 412, 410, 395, 394, 313, 286, 285, 272, 271 and 257

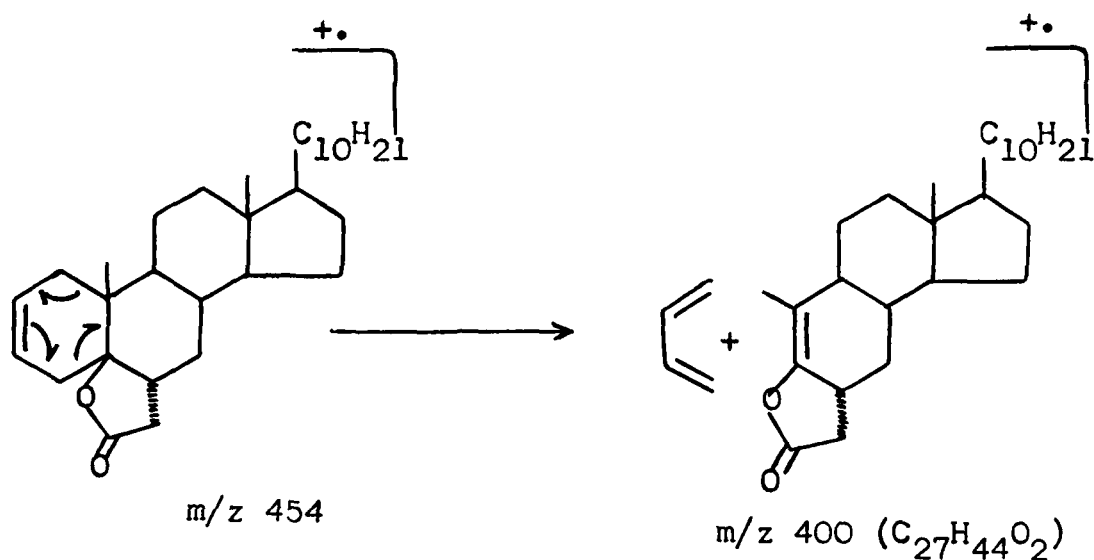
Scheme - 31





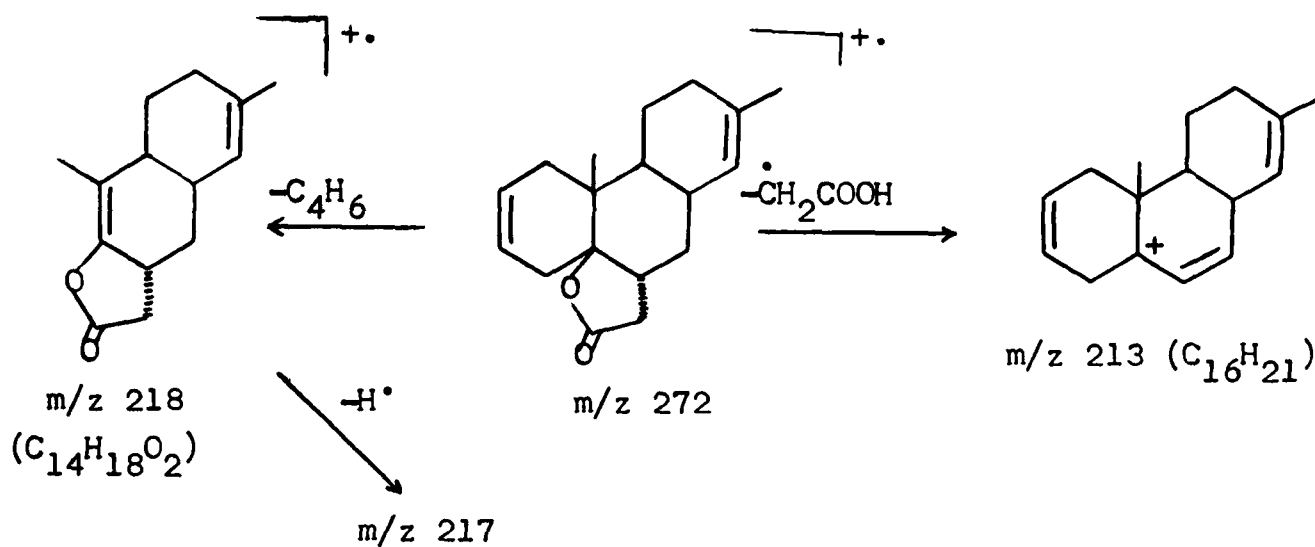
This important ion may be shown to arise from the ion m/z 454 by the loss of a molecule of butadiene in a retro Diels-Alder fashion.

Scheme - 32



m/z 218, 217 and 213

Scheme - 33



The mass spectrum of the compound (CCLXXIX) (Fig. 11) gave the highest mass peak at m/z 452 ($C_{31}H_{48}O_2$) which can be explained to be obtained from the molecular ion M^+ 512 ($C_{33}H_{52}O_4$) by the loss of acetic acid, followed by other peaks at m/z 410 (m/z 452- $CH_2=C=O$), 408 (m/z 452- CO_2), 393 (m/z 452- CH_2COOH), 392, 311 (m/z 452- $C_{10}H_{21}$), 284 (m/z 452-168), 283, 270 (m/z 452-172), 269, 255 (m/z 270- CH_3), 225 (m/z 269-44), 211 (m/z 270-59), 210 and lower mass peaks. This observation is easily comparable with the mass spectrum of the compound (CCXCIII) (Fig. 10). It is pertinent to mention here that as expected the loss of C_4H_6 moiety from ring A is not observed. The following scheme shows the formation of some important fragment ion.

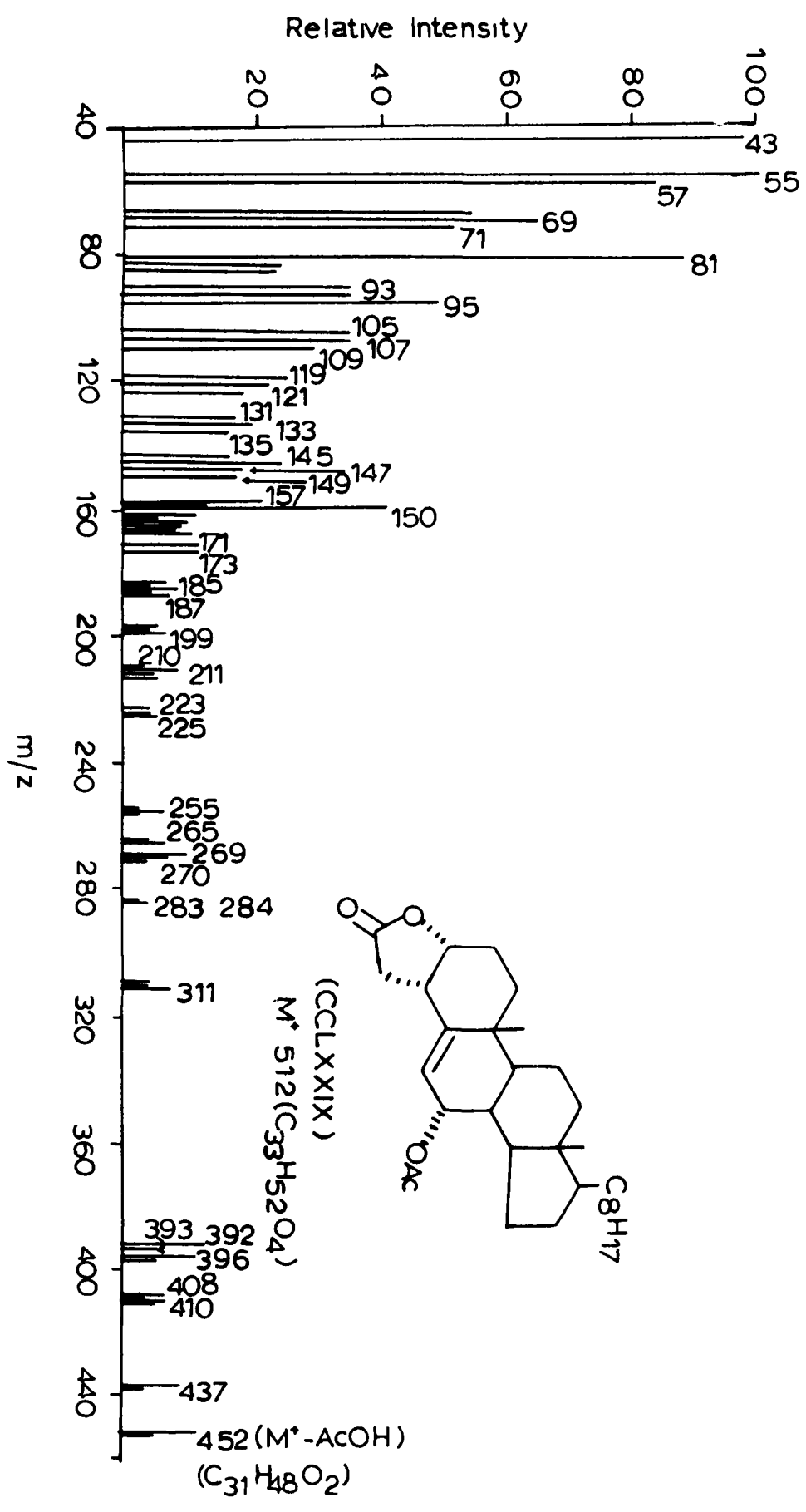
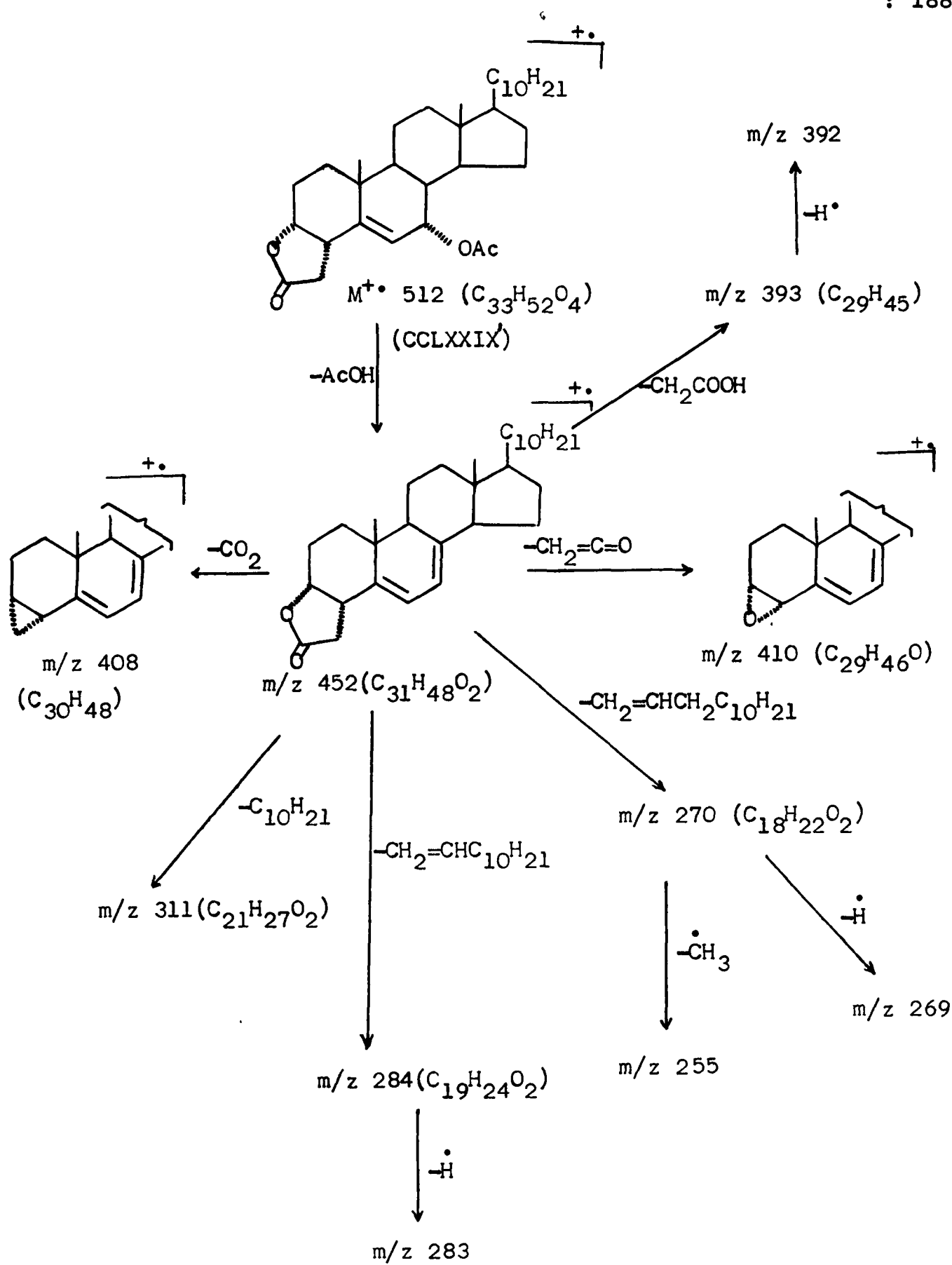


Fig. 11



EXPERIMENTAL

All melting points are uncorrected. IR spectra were determined in nujol with a Perkin-Elmer 621 and Pye Unicam SP3-100 spectrophotometer. UV spectra were recorded in methanol on a Pye-Unicam PU-8800 spectrophotometer. NMR spectra were run in CDCl_3 on a Varian A-60D instrument with TMS as internal standard. Mass spectra were measured on JMS-D300 spectrometer using direct insertion technique at a source temperature of 250° . Thin layer chromatographic plates were coated with silica gel G and sprayed with 20% aqueous perchloric acid. Light petroleum refers to a fraction of b.p. $60-80^\circ$. NMR values are given in ppm (s= singlet, d= doublet, t= triplet, br= broad, dd= doublet of a doublet, mc= multiplet centred at). IR values are given in cm^{-1} (s= strong, m= medium, w= weak, br= broad). UV values are given in nm.

5-Cholesten- 3β -yl chloride

Freshly prepared thionyl chloride (40 ml) was added gradually to cholesterol (50 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at temperature of $50-60^\circ$ on a water bath for one hour and then poured onto crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice cooled water and air dried. Recrystallization from acetone gave 5-cholesten- 3β -yl chloride (45 g), m.p. $95-96^\circ$ (lit.¹²⁹ m.p. $96-97^\circ$).

5-Cholestene

5-Cholesten-3 β -yl chloride (10 g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (20 g) was added to the solution with continuous stirring over a period of eight hours. The reaction mixture was warmed occasionally when all the sodium metal was dissolved, the reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand overnight. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. The crude material was recrystallized from acetone to provide 5-cholestene as cubes (8.3 g), m.p. 94° (lit.¹³⁰ m.p. 95°).

6-Nitro-5-cholestene

A suspension of powdered 5-cholestene (6 g) in glacial acetic acid (50 ml) was vigorously stirred at room temperature and treated with nitric acid (15 ml; d, 1.5), followed by the addition of sodium nitrite (3 g) over a period of one hour. The reaction mixture was poured into cold water and the yellow product thus obtained was extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (10%) (until the washings were pink) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired compound as an oil which was crystallized from ethanol as leaflets (4.5 g), m.p. 119 (lit.¹³¹ m.p. 120-121°).

6-Oxo-5 α -cholestane

6-Nitro-5-cholestene (6 g) was dissolved in warm glacial acetic acid (120 ml) and zinc dust (12 g) was gradually added with shaking. The mixture was heated under reflux for four hours and water (12 ml) was added now and then during the course of reaction. Unreacted zinc was removed by filtration and the filtrate was diluted with water. 6-Oxo-5 α -cholestane crystallized out as thin plates and was recrystallized from ethanol (3.5 g), m.p. 96-98° (lit.¹³² m.p. 98-100°).

6-Oxocholestan-5 α -yl bromide

6-Oxo-5 α -cholestane (8 g) was dissolved in acetic acid (18 ml) and ether (91 ml) and cooled to 0°. Bromine solution (4.1 g of bromine in 58 ml of acetic acid) was added to it slowly. Few drops of hydrobromic acid were added to catalyse the reaction. Decolourisation proceeded rapidly, and a crystalline material started separating after the addition of approximately half of the bromine solution. The ether was removed under reduced pressure, and the desired bromo ketone, collected by filtration, was recrystallized from light petroleum (3.6 g), m.p. 102° (lit.¹³³ m.p. 101-102°).

4-Cholesten-6-one (CCXII)

A solution of 6-oxocholestan-5 α -yl bromide (5 g) in pyridine (50 ml) was heated under reflux for eight hours under

anhydrous conditions. The mixture was diluted with ice cooled water and extracted with ether. The ethereal solution was washed with water, dilute hydrochloric acid, sodium bicarbonate (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave (CCXII) as an oil which was recrystallized from methanol (2.7 g), m.p. 108° (lit.¹⁰⁸ m.p. $108-109^{\circ}$).

Reaction of 4-cholesten-6-one (CCXII) with phenylhydrazine
(under atmospheric conditions): 2'-phenyl-4-cholesteno[4,6-cd]-
pyrazole (CCXXI)

A solution of the ketone (CCXII)¹⁰⁸ (1 g) in benzene (30 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml). The reaction mixture was heated under reflux for about three hours. The benzene was removed under reduced pressure and the residue thus obtained was extracted with ether. The ethereal solution was washed successively with water, sodium bicarbonate (5%) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (35:1) gave 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI) which was recrystallized from methanol (400 mg), m.p. 152° . ν_{\max} 3050 (aromatic C-H), 1600 and 690 (monosubstituted benzene), 1500 (C=N); δ 7.48 br, m (5H, C₆H₅), 2.8 br, m (2H, C₇-H₂), 1.9 br, m (2H, C₃-H₂), 1.1 (C₁₀-Me), 0.73 (C₁₃-Me), 0.93 and 0.83 (other methyl protons); λ_{\max} 268 nm (pyrazole moiety); M^{+} 472 (C₃₃H₄₈N₂).

Analysis Found : C, 83.6; H, 9.9; N, 5.2.

$C_{33}H_{48}N_2$ requires : C, 83.9; H, 10.2; N, 5.9%.

Reaction of 4-cholesten-6-one (CCXII) with phenylhydrazine (under nitrogen atmosphere): 2'-phenyl-5 α -cholestan[4,6-cd]-pyrazoline (CCXXII); 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI) and 2'-phenyl-5-cholesteno[6,4-cd]-pyrazole (CCXXIII)

The ketone (CCXII)¹⁰⁸ (1.0 g) was dissolved in dry benzene (30 ml) and to this solution were added phenylhydrazine (2 ml) and glacial acetic acid (2 ml). After bubbling the nitrogen gas into the reaction flask for 3-5 minutes, the contents were allowed to reflux under the same conditions for three hours. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water, dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which on rapid column chromatography over silica gel (30 g), on elution with light petroleum-ether (50:1) gave 2'-phenyl-5 α -cholestan[4,6-cd]-pyrazoline (CCXXII) as an oil (400 mg); ν_{\max} 3070, 740, 690 (mono-substituted benzene), 1600, 1500 (pyrazoline moiety); δ 6.9 br,m (5H, C₆-H₅), 4.2 br,m (1H, C₄-H), 2.7 d (J=12 Hz, 2H, C₇-H₂), 1.1 (C₁₀-Me), 0.63 (C₁₃-Me), 0.9 and 0.8 (other methyls).

Analysis Found : C, 83.2 ; H, 10.1 ; N, 5.6.

$C_{33}H_{50}N_2$ requires : C, 83.48; H, 10.61; N, 5.90%.

Further elution with light petroleum-ether (35:1) gave 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI) (300 mg) , m.p.152°.

Further elution (15:1) gave 2'-phenyl-5-cholesteno[6,4-cd]-pyrazole (CCXXIII) as non-crystallizable oil (200 mg); ν_{\max} 3060 w, 1600 s, 1500 s, 760 and 690 cm^{-1} (phenylpyrazole); δ 7.5 br,m (5H, $\text{C}_6\text{-H}_5$), 2.8 br,m (2H, $\text{C}_3\text{-H}_2$), 1.9 br,m (2H, $\text{C}_7\text{-H}_2$), 1.10 ($\text{C}_{10}\text{-Me}$), 0.70 ($\text{C}_{13}\text{-Me}$), 0.9 and 0.8 (other methyls); λ_{\max} 267 nm.

Analysis Found : C, 83.4; H, 9.8 ; N, 5.5.

$\text{C}_{33}\text{H}_{48}\text{N}_2$ requires : C, 83.9; H, 10.23; N, 5.92%.

Oxidation of 2'-phenyl-5 α -cholestan[4,6-cd]-pyrazoline (CCXXII):

2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI)

The pyrazoline (CCXXII) (800 mg) was dissolved in benzene (25 ml) and a few crystals of freshly prepared lead tetraacetate were added to it. The reaction mixture was heated on water bath for 20 minutes and the solvent was removed under reduced pressure. The organic matter was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Removal of the solvent gave a semi-solid which was crystallized from methanol to give the pyrazole (CCXXI) (250 mg) m.p. and m.m.p.152°.

5-Cholesten-3 β -yl acetate

A mixture of cholesterol (50 g), pyridine (75 ml) and acetic anhydride (50 ml) was heated on a steam bath for two hours. The resulting brown solution was poured onto crushed ice-water mixture with stirring. A light brown solid was obtained, which was filtered under suction, washed with water until free from pyridine and air dried. The crude product on recrystallization from acetone gave the pure acetate (45 g), m.p.114-115° (lit.¹³⁴ m.p.116°).

6-Nitro-5-cholesten-3 β -yl acetate

5-Cholesten-3 β -yl acetate (5 g) was covered with nitric acid (125 ml; d, 1.52) and sodium nitrite (5 g) was gradually added over a period of one hour with continuous stirring. Slight external cooling was also affected during the course of the reaction. Stirring was continued for additional two hours when a yellow spongy mass separated on the surface of the mixture. The mixture was diluted with cold water (100 ml) when a green colour solution was obtained. The whole mass was extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided the nitro compound as an oil, crystallized from methanol (3.5 g), m.p.104° (lit.¹³⁰ m.p.102-104°).

6-Oxo-5 α -cholestan-3 β -yl acetate

6-Nitro-5-cholesten-3 β -yl acetate (3 g) was dissolved in glacial acetic acid (125 ml) by warming the mixture. Zinc dust (6 g) was added in small portions with shaking. The suspension was heated under reflux for four hours and water 6 ml was added now and then during the course of the reaction. The hot solution was filtered, cooled to room temperature and diluted with excess of ice cooled water. The precipitate thus obtained was taken in ether and the ethereal solution was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the desired ketone as oil which was crystallized from methanol (2.1 g) m.p.128-129° (lit.¹³⁵ m.p.128-129°).

6-Oxo-5 α -bromocholestan-3 β -yl acetate

To a cooled solution of 6-oxo-5 α -cholestan-3 β -yl acetate (2 g) in acetic acid (5 ml) and ether (18 ml), bromine solution (1.1 g of bromine in 15 ml of acetic acid) was added gradually with shaking. Few drops of hydrobromic acid were added to catalyse the reaction. The bromo compound that precipitated out was filtered and recrystallized from chloroform-ether (1.2 g), m.p.162-164° (lit.¹¹⁴ m.p.162°).

6-Oxo-4-cholesten-3 β -yl acetate (CCXIII)

A solution of 6-oxo-5 α -bromocholestan-3 β -yl acetate (2 g) and pyridine (20 ml) was heated under reflux for eight hours under anhydrous conditions. The reaction mixture was poured into ice cooled water acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was recrystallized from methanol to give the ketone (CCXIII) (1.5 g), m.p. 106-108° (lit.¹¹⁴ m.p. 110°).

Reaction of 6-oxo-4-cholesten-3 β -yl acetate (CCXIII) with phenylhydrazine (under atmospheric conditions): 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV)

The ketone (CCXIII) (1.0 g) in benzene (25 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml) and the reaction mixture was heated under reflux for four hours. Benzene was removed under reduced pressure and the residue was extracted with ether. After usual work up and removal of the solvent gave a semi-solid material which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (40:1) gave a solid (CCXXV) which was recrystallized from methanol (380 mg) m.p. 226°; ν_{\max} 3050, 1600, 750, 690 (characteristic of monosubstituted benzene), 1680 (-C=C-C=O), 1490 (C=N); δ 7.5 br, m (5H, aromatic), 2.3 m (2H, $\text{C}_2\text{-H}_2$),

2.75 br (2H, C₇-H₂), 1.2 (C₁₀-Me), 0.66 (C₁₃-Me), 1.1, 0.8 and 0.72 (other methyls); λ_{\max} 310, 258 and 226 nm; M⁺ 486 (C₃₃H₄₆N₂O).

Analysis Found : C, 81.1; H, 9.2; N, 2.9.

C₃₃H₄₆N₂O requires : C, 81.5; H, 9.5; N, 2.9%.

Reaction of 6-oxo-4-cholesten-3 β -yl acetate (CCXIII) with phenylhydrazine (under nitrogen atmosphere): 2'-phenyl-3-cholesteno [4,6-cd]-pyrazoline (CCXXXI), 3-oxo-2'-phenyl-5 β -cholestan[4,6-cd]-pyrazoline (CCXXXII) and 3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV)

The ketone (CCXIII) (1.0 g) was dissolved in dry benzene (30 ml) and to this solution was added phenylhydrazine (2 ml) and glacial acetic acid (2 ml). The contents were heated under reflux in nitrogen atmosphere for three hours. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and again with water, and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which on rapid column chromatography over silica gel (30 g), on elution with light petroleum-ether (50:1) afforded (CCXXXI) as an oil (200 mg); ν_{\max} 3040, 1590, 1480, 765 and 685 (phenylpyrazole) and 1620 cm⁻¹ (C=C); δ 7.5 br,m (5H, C₆-H₅), 5.8 br (1H, C₃-vinylic H), 2.7 br,m (2H, C₇-H₂), 1.8 m (2H, C₂-H₂), 1.2 (C₁₀-Me), 0.7 (C₁₃-Me), 1.1, 0.9 and 0.8 (other methyls).

Analysis Found : C, 83.4 ; H, 10.0 ; N, 5.4.

$C_{33}H_{48}N_2$ requires : C, 83.84; H, 10.23; N, 5.92%.

Further elution with light petroleum-ether (45:1) gave pyrazoline (CCXXXII) as a non-crystallizable oil (150 mg); ν_{\max} 3060, 1600, 1500, 750, 690 (phenylpyrazoline) and 1705 cm^{-1} (C_3 -oxo group). Further spectral studies of the compound were not possible due to its very unstable nature when in contact with air and completely oxidized to (CCXXV).

Further elution with light petroleum-ether (40:1) gave (CCXXV) (300 mg) m.p. and m.m.p. 226° [Identical in all respects to the compound (CCXXV) obtained as the only product by the same reaction under atmospheric conditions].

Isomerization of (CCXXXI) to (CCXXI)

The compound (CCXXXI) (100 mg) obtained from the reaction of the ketone (CCXIII) under nitrogen was dissolved in benzene (15 ml) and to this was added sodium methoxide solution (20 ml). The reaction mixture was heated under reflux for one hour. Removal of the solvent and usual work up gave the pyrazole (CCXXI), which was crystallized from methanol (65 mg) m.p. and m.m.p. 152° .

$3\beta,5,6\beta$ -Trihydroxy- 5α -cholestane

A mixture of cholesterol (20 g) and formic acid (20 ml; 88%) was heated on a water bath for five minutes and then allowed

to attain room temperature. Hydrogenperoxide (20 ml; 30%) was added to the mixture and it was kept at the room temperature for two hours with occasional shaking. Boiling water (300 ml) was added to the mixture with stirring and the reaction mixture allowed to attain room temperature, when a white solid separated which was filtered under suction and air dried. The solid was dissolved in methanol (600 ml) and heated with aqueous sodium hydroxide solution (20 ml; 25%) for 10 minutes on a steam bath. It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration under reduced pressure and recrystallized from methanol (18 g), m.p. 237-239° (lit.¹³⁶ m.p. 237-239°).

3,6-Dioxo-5 α -hydroxycholestane

A suspension of 3 β ,5,6 β -trihydroxy-5 α -cholestane (5 g) in acetone (200 ml) was cooled in an ice bath. Jones' reagent (15 ml) was added gradually with stirring over a period of 30 minutes. Water (200 ml) was added to the reaction mixture and the precipitate thus obtained was collected by filtration under suction. The crude product was subjected to column chromatography over silica gel (100 g). Elution with chloroform gave the dione which was recrystallized from methanol (3.2 g) m.p. 237-239° (lit.¹¹⁶ m.p. 237-239°).

4-Cholestene-3,6-dione (CCXIV)

A mixture of 3,6-dioxo-5 α -hydroxycholestane (2 g), dioxan (140 ml) and sulphuric acid (2 ml) was heated under reflux for one hour. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ether. The ethereal solution was successively washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired enedione (CCXIV), recrystallized from light petroleum (1.4 g), m.p. 122-123° (lit.¹¹⁶ m.p. 122-123°); ν_{\max} 1680 (C=C-C=O) and 1600 cm⁻¹ (C=C); δ 6.08 s (1H, C₄-vinyllic H), 2.4 m (4H, C₂-H₂ and C₇-H₂), 1.2 (C₁₀-Me), 0.7 (C₁₃-Me), 0.9 and 0.85 (other methyl protons).

Reaction of 4-cholestene-3,6-dione (CCXIV) with phenylhydrazine:3-oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV)

The ketone (CCXIV)¹¹⁶ (1.0 g) in benzene (25 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml) and the mixture was heated under reflux for four hours. Usual work up and removal of the solvent gave a semi-solid material which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (40:1), yielded (CCXXV) which was crystallized from methanol (380 mg), m.p. 226° [identical with the sample obtained in earlier experiments].

2,4-Cholestadien-6-one (CCXV)

6-Oxo-4-cholesten-3 β -yl acetate (CCXIII) (5 g) was dissolved in ethanol (100 ml) and dilute hydrochloric acid (5 ml). The reaction mixture was heated under reflux for two hours. On cooling, a solid was obtained which was filtered and recrystallized from methanol to give (CCXV) (3.2 g), m.p. 127° (lit.¹⁰⁸ m.p. 128-129°). ν_{\max} 3120 (C=C-H), 1670 (-C=C-C=O) and 1625 cm⁻¹ (C=C); δ 6.6 mc (1H, C₂-H), 5.96 dist. d (2H, C₂-H and C₄-H), 2.3 br, m (2H, C₇-H₂), 1.2 (C₁₀-Me), 0.75 (C₁₃-Me), 0.9 and 0.88 (other methyls); λ_{\max} 316 nm.

Reaction of 2,4-cholestadien-6-one (CCXV) with phenylhydrazine:2'-phenyl-2,4-cholestadieno[4,6-cd]-pyrazole (CCXXXIII)

The ketone (CCXV) (1 g) in benzene (30 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml) and the reaction mixture was heated under reflux for three hours. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave a semi-solid which was chromatographed over silica gel (40 g).

Eluates with light petroleum-ether (35:1) on recrystallization from methanol gave (CCXXXIII) (400 mg), m.p. 178°. ν_{\max} 3060,

1600, 1500, 760 and 680 cm^{-1} (phenyl pyrazole); δ 7.3 br,m (5H, $\text{C}_6\text{-H}_5$), 6.58 d (1H, $\text{C}_3\text{-H}$, $J=9\text{ Hz}$), 5.8 br,m (1H, $\text{C}_2\text{-H}$), 2.16 br,m (2H, $\text{C}_7\text{-H}_2$), 1.8 br,m (2H, $\text{C}_1\text{-H}_2$), 1.2 ($\text{C}_{10}\text{-Me}$), 0.75 ($\text{C}_{13}\text{-Me}$), 1.05, 0.9 and 0.83 (other methyls); λ_{max} 260 nm; M^{+} 470 ($\text{C}_{33}\text{H}_{46}\text{N}_2$).

Analysis Found : C, 84.18; H, 9.75; N, 5.86.

$\text{C}_{33}\text{H}_{46}\text{N}_2$ requires : C, 84.19; H, 9.84; N, 5.95%.

3 β -Hydroxy-5 α ,6 β -dibromocholestane

To a solution of cholesterol (5 g) in ether (30 ml) was added bromine solution (0.9 ml of bromine in 20 ml glacial acetic acid containing 0.2 g of anhydrous sodium acetate) with stirring. The solution turned yellow and promptly set to a stiff paste of the dibromide. The mixture was cooled in ice bath and stirred with a glass rod to ensure complete crystallization. The product was then collected by filtration under suction and washed with cold acetic acid-ether until the filtrate was completely colourless (6.9 g), m.p. 112-113° (lit.¹¹⁷ m.p. 113°).

5,6 β -Dibromo-5 α -cholestan-3-one

The moist dibromide (6.9 g) was suspended in acetone (150 ml) in a three necked round bottom flask fitted with a stirrer and dropping funnel. The suspension was stirred for five minutes and Jones' reagent (10 ml) was then added in drops from dropping funnel in 15 minutes. The temperature of the reaction

mixture during oxidation, was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for 15 minutes and cold water (200 ml) was added. The product was collected on a Buchner funnel and washed thoroughly with water and methanol and air dried (5 g), m.p.73-75° (decomposition) (lit.¹¹⁷ m.p.73-75°).

5-Cholesten-3-one

To a solution of 5,6 β -dibromo-5 α -cholestan-3-one (5 g) in ether (100 ml) and acetic acid (2.5 ml) was added zinc dust (7.5 g) in small portions over a period of one hour, with continuous shaking. After the addition was complete, the ethereal solution containing suspended zinc dust was filtered. The ethereal phase was then washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was crystallized from methanol to give the desired ketone (3.2 g), m.p.127-128° (lit.¹¹⁷ m.p.129°).

4-Cholesten-3-one (CCXVI)

A solution of 5-cholesten-3-one (5 g) in ethanol (50 ml) containing oxalic acid (0.6 g) was heated under reflux for 15 minutes. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous

sodium sulphate. Evaporation of the solvent gave an oil which was crystallized from ethanol in the cold to give the ketone (CCXVI), (3.8 g), m.p. 80-81° (lit.¹¹⁷ m.p. 81-82°).

Reaction of 4-cholesten-3-one (CCXVI) with phenylhydrazine:

4-cholesten-3-one phenylhydrazone (CCXXXIV)

The ketone (CCXVI) (1 g) was dissolved in warm methanol (30 ml). To this was added p-toluenesulphonic acid (catalytic amount) and phenylhydrazine (1 ml). The contents were heated under reflux for one hour. A solid separated after cooling which was filtered under suction and air dried. The solid was recrystallized from methanol to give the phenylhydrazone (CCXXXIV) (800 mg), m.p. 144°. ν_{\max} 3330-3420 br ($-\text{NH}-\text{Ph}$), 3030, 1600 (aromatic C-H), 1590 and 1495 cm^{-1} (C=N); δ 7.2 br, m (5H, C_6-H_5), 6.3 s (1H, C_6-H), 2.3 br, m (2H, C_2-H_2), 1.1 ($\text{C}_{10}-\text{Me}$), 0.72 ($\text{C}_{13}-\text{Me}$), 0.96, 0.83 and 0.78 (other methyls).

Analysis Found : C, 83.30; H, 10.51; N, 5.75.

$\text{C}_{33}\text{H}_{50}\text{N}_2$ requires : C, 83.48; H, 10.63; N, 5.90%.

Reaction of 4-cholesten-3-one phenylhydrazone (CCXXXIV) with acetic acid: 6-oxo-5 α -3-cholesteno[3,4]-N,N-phenylhydrazine (CCXXXV)

4-Cholesten-3-one phenylhydrazone (CCXXXIV) (700 mg) was dissolved in benzene (15 ml) and acetic acid (5 ml) and the reaction mixture was heated under reflux for two hours. The solvents

were removed under reduced pressure and the semi-solid material thus obtained was dissolved in ether, washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (20 g). Elution with light petroleum-ether (22:1) afforded the compound (CCXXXV), recrystallized from methanol (110 mg), m.p. 185°. ν_{\max} 3260 br (C-N-H), 1715 s (C=O), 1650, 1530 and 1460 cm^{-1} (C=C-N-N-); δ 9.9 br, s (1H, N-H), 7.4 br, m (5H, C₆-H₅), 3.7 s (1H, C₅-αH), 2.67 d (2H, C₇-H₂, J=10 Hz), 1.3 (C₁₀-Me), 0.65 (C₁₃-Me), 1.2, 0.9 and 0.8 (other methyls); M^{+} 488 (C₃₃H₄₈N₂O).

Analysis Found : C, 83.68; H, 10.06; N, 5.78.

C₃₃H₄₈N₂O requires : C, 83.84; H, 10.23; N, 5.93%.

6β-Bromo-4-cholesten-3-one (CCXVII)

5,6β-Dibromo-5α-cholestan-3-one (5 g) was dissolved in absolute methanol (100 ml) by warming on a water bath. Anhydrous potassium acetate (2.5 g) was added to the above solution and the mixture was heated under reflux for two hours. The resulting light yellow coloured solution was poured into crushed ice water mixture and the white precipitate thus obtained was extracted with ether, washed several times with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 6β-bromo-4-cholesten-3-one (CCXVII) as an oil which was crystallized from methanol

(2.2 g), m.p.132° (lit.^{117a} m.p.132°). γ_{\max} 1680 (C=C-C=O), 1620 (C=C) and 740 cm⁻¹ (C-Br); δ 5.85 s (1H, C₄-vinylic H), 4.9 m (1H, C₆- α H, W_{1/2}=7 Hz), 1.2 (C₁₀-Me), 0.91, 0.83 and 0.8 (other methyls).

Reaction of 6 β -bromo-4-cholesten-3-one (CCXVII) with phenylhydrazine: 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole-3-one phenylhydrazone (CCXXXVII) and 2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV)

The ketone (CCXVII)^{117a} (2 g) was dissolved in benzene (30 ml) and to this was added phenylhydrazine (2.5 ml) and acetic acid (2 ml). The reaction mixture was then heated under reflux for six hours. Benzene was removed by distillation under reduced pressure. The residue was extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave oily material which was chromatographed over silica gel (50 g). Elution with light petroleum-ether (50:1) furnished the compound (CCXXXVII) which on recrystallization from methanol afforded fine orange colour crystals, 400 mg, m.p.195°.

γ_{\max} 3240 m (N-H), 1605 (C=C), 1590, 1480 (C=N), 750 and 695 cm⁻¹; δ 7.1-7.5 m (10H, 2xC₆-H₅), 12.7 s (1H, N-H), 2.9 m (2H, C₂-H₂), 2.25 d (2H, C₇-H₂; J=10 Hz), 1.2 (C₁₀-Me), 0.73 (C₁₃-Me), 0.9 and 0.8 (other methyls); M⁺ 576 (C₃₉H₅₂N₄).

Analysis Found : C, 81.2; H, 9.2; N, 9.4.

$C_{39}H_{52}N_4$ requires : C, 81.3; H, 9.0; N, 9.7%.

Further elution with light petroleum-ether (40:1) afforded the pyrazole (CCXXV), recrystallized from methanol (300 mg) m.p. and m.m.p. 226°.

5-Stigmasten-3 β -yl chloride (CCLXI)

Freshly purified thionyl chloride (40 ml) was added gradually to β -sitosterol (50 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at temperature of 50-60° on a water bath for one hour, and then poured onto crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice cooled water and air dried. Recrystallization from acetone gave 5-stigmasten-3 β -yl chloride (CCLXI) (45 g), m.p. 82° (lit.¹²⁸ m.p. 82°).

5-Stigmastene (CCLX)

5-Stigmasten-3 β -yl chloride (CCLXI) (10 g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (20 g) was added to the solution with continuous stirring over a period of eight hours. The reaction mixture was warmed occasionally, when all the sodium was dissolved the reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand overnight. A white

crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. The crude material was recrystallized from acetone to provide 5-stigmastene (CCLX) (8 g), m.p. 75° (lit.¹²⁸ m.p. 75°).

4-Stigmasten-6-one (CCXVIII)

5-Stigmastene (CCLX) (12 g) was dissolved in ether (200 ml) and to this was added at 0° , perchloric acid (1.6 ml) and N-bromo-succinamide (9.6 g). The mixture was stirred at room temperature for two hours. The reaction mixture was then extracted with ether. Ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a semi-solid material (9 g). Semi-solid was suspended in acetone (300 ml), Jones' reagent (15 ml) was added and the reaction mixture was stirred at $5-10^{\circ}$ for two hours. Excess of the chromic acid was destroyed by isopropanol and saturated solution of sodium acetate. Ice cooled water (200 ml) was added to the reaction flask. A sticky material separated out which was filtered and taken in pyridine (70 ml) and heated under reflux for eight hours under anhydrous conditions. The mixture was diluted with ice cooled water and extracted with ether. Ethereal layer was washed with water, dilute hydrochloric acid, sodium bicarbonate (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed over silica gel (60 g). Elution with light petroleum-ether (30:1)

gave 4-stigmasten-6-one (CCXVIII), recrystallized from methanol (3.0 g), m.p. 104°. ν_{\max} 1680 (C=C-C=O) and 1620 cm^{-1} (C=C-); δ 6.25 t (1H, C₄-vinylic H), 2.13 br, m (2H, C₇-H₂), 1.9 br, m (2H, C₃-allylic), 1.1 (C₁₀-Me), 0.7 (C₁₃-Me), 0.96, 0.90 and 0.8 (other methyl protons).

Reaction of 4-stigmasten-6-one (CCXVIII) with phenylhydrazine:

2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXL)

A solution of 4-stigmasten-6-one (CCXVIII) (1.5 g) in benzene (30 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml). The reaction mixture was heated under reflux for three hours. Benzene was removed under reduced pressure and the residue thus obtained was extracted with ether. Usual work up of the ethereal solution and removal of the solvent gave an oil, which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (30:1) gave (CCXL), recrystallized from methanol (500 mg), m.p. 132°. ν_{\max} 3015 w, 1600 s, 1500, 760 and 690 cm^{-1} (phenylpyrazole moiety); δ 7.47 br, m (5H, C₆-H₅), 2.83 br, m (2H, C₇-H₂), 2.0 br, m (2H, C₃-H₂), 1.2 (C₁₀-Me), 0.7 (C₁₃-Me), 1.1 and 0.9 (other methyl protons); λ_{\max} 260 nm; M^{+} 500 (C₃₅H₅₂N₂).

Analysis Found : C, 83.8 ; H, 10.3 ; N, 5.4.

C₃₅H₅₂N₂ requires : C, 83.94; H, 10.46; N, 5.59%.

5-Stigmasten-3 β -yl acetate (CCLXII)

A mixture of β -sitosterol (100 g), pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a water bath for two hours. A brown solution was obtained which after cooling was poured onto crushed ice water mixture with stirring. The white precipitate thus obtained was filtered under suction, washed with water and air dried. The crude acetate was recrystallized from acetone (90 g), m.p. 120° (lit.¹²⁸ m.p. 120°).

6-Nitro-5-stigmasten-3 β -yl acetate

To a cooled mixture of 5-stigmasten-3 β -yl acetate (CCLXII) (10 g) and nitric acid (200+50 ml fuming nitric acid) was added sodium nitrite (10 g) in portions with constant stirring over a period of about 45 minutes. After complete addition of sodium nitrite stirring was continued for additional two hours. Cold water (about 350 ml) was added to the reaction mixture when a solid material separated. Organic matter was dissolved in ether and the ethereal layer was washed with water, sodium bicarbonate solution (5%) (until the washing became pink) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was crystallized from methanol to afford 6-nitro-5-stigmasten-3 β -yl acetate (7 g), m.p. 79° (lit.¹²⁸ m.p. 79°).

6-Oxo-5 α -stigmastan-3 β -yl acetate

A mixture of 6-nitro-5-stigmasten-3 β -yl acetate (10 g), acetic acid (200 ml), zinc dust (20 g) and water (20 ml) was heated under reflux for four hours. Zinc dust was removed by filtration and the filtrate was diluted with large excess of water. The organic matter was extracted with ether, washed successively with water and sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave 6-oxo-5 α -stigmastan-3 β -yl acetate, recrystallized from methanol (6.5 g), m.p.120° (lit.¹²⁸ m.p.120°).

6-Oxo-5 α -bromostigmastan-3 β -yl acetate

Bromine solution in acetic acid (20 ml, 5%) was slowly added to a solution of 6-oxo-5 α -stigmastan-3 β -yl acetate (2 g) in ether (20 ml) in presence of hydrobromic acid as the catalyst. Decolourization proceeded rapidly and the crystalline material separated after the addition of approximately half of the bromine solution. The reaction mixture was further allowed to stand at 0° for one hour, to ensure complete crystallization. The solid was filtered under suction and recrystallized from light petroleum to give the desired bromo ketone (1.2 g), m.p.201° (lit.¹²⁸ m.p.201°).

6-Oxo-4-stigmasten-3 β -yl acetate (CCXIX)

A mixture of 6-oxo-5 α -bromostigmastan-3 β -yl acetate (2 g) and pyridine (25 ml) was heated under reflux for six hours under anhydrous conditions, then it was poured into ice cooled water acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was crystallized from methanol to give the ketone (CCXIX) (1.2 g), m.p. 115° (lit.¹²⁸ m.p. 115°); ν_{\max} 1735 (CH₃COO), 1680 (C=C-C=O) and 1240 cm⁻¹ (acetate); δ 6.03 d (1H, C₄-vinylic H, J=3 Hz), 2.03 (CH₃COO), 1.1 (C₁₀-Me), 0.68 (C₁₃-Me), 0.9, 0.8 and 0.75 (other methyls). λ_{\max} 220 nm.

Reaction of 6-oxo-4-stigmasten-3 β -yl acetate (CCXIX) with phenylhydrazine: 3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII)

The ketone (CCXIX) (1 g) in benzene (25 ml) was treated with phenylhydrazine (2 ml) acetic acid (2 ml) and the reaction mixture was heated under reflux for four hours. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water. Removal of the solvent gave semi-solid material, which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (30:1) yielded (CCXLII) which was

crystallized from methanol (300 mg), m.p. 147°. ν_{\max} 1680 s ($\text{C}=\text{C}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$), 1600 w, 760, 690 (monosubstituted benzene) and 1500 cm^{-1} ($\text{C}=\text{N}$); δ 7.5 br, m (5H, C_6-H_5), 2.83 br, m (2H, C_7-H_2), 2.5 br, m (2H, C_2-H_2), 1.2 ($\text{C}_{10}-\text{Me}$), 0.7 ($\text{C}_{13}-\text{Me}$), 1.1 and 0.9 (other methyl protons); λ_{\max} 260 and 285 nm; M^{+} 514. ($\text{C}_{35}\text{H}_{50}\text{N}_2\text{O}$).

Analysis Found : C, 80.9 ; H, 9.6 ; N, 5.2.

$\text{C}_{35}\text{H}_{50}\text{N}_2\text{O}$ requires : C, 81.66; H, 9.78; N, 5.44%.

4-Stigmastene-3,6-dione (CCXX)

β -Sitosterol (10 g) was suspended in acetone (300 ml) in a three neck round bottom flask fitted with a stirrer and a dropping funnel. The suspension was stirred for about 30 minutes and then Jones' reagent (25 ml) was added dropwise from the dropping funnel in a course of 45 minutes. The temperature of the reaction mixture, was maintained at 0-5° by external cooling. After the addition was complete, stirring was continued for additional 30 minutes, and then cold water (200 ml) was added. The product was collected by filtration and washed thoroughly with water and air dried. The crude product was recrystallized from acetone to give (CCXX) (2.2 g), m.p. 156°. ν_{\max} 1675 ($-\text{C}=\text{C}-\text{C}=\text{O}$) and 1610 cm^{-1} ($\text{C}=\text{C}$); δ 6.1 s (1H, C_6 -vinylic H), 2.4 m (4H, C_2-H_2 and C_7-H_2), 1.2 ($\text{C}_{10}-\text{Me}$), 0.70 ($\text{C}_{13}-\text{Me}$), 1.1, 0.95 and 0.81 (other methyl protons).

Reaction of 4-stigmastene-3,6-dione (CCXX) with phenylhydrazine:
3-oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII)

The dienone (CCXX) (1.5 g) was dissolved in benzene (30 ml) and treated with phenylhydrazine (2 ml) and acetic acid (2 ml) and the reaction mixture was refluxed for four hours. Removal of the solvent and usual work up gave a semi-solid, which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (35:1) gave (CCXLII) which was recrystallized from methanol (400 mg) m.p. and m.m.p. 147°.

Reaction of 4-cholestene-3,6-dione (CCXIV) with ethylacetoacetate:
2'-methyl-3'-carboethoxy-3-oxo-5-cholesteno[4 α ,6-de]- γ -pyran(CCXLVI)

The ketone (CCXIV)¹¹⁶ (1 g) was dissolved in ethylacetoacetate (10 ml) and was added to a well stirred solution of fused zinc chloride (1 g) in acetic acid (10 ml) and acetic anhydride (10 ml). Colour of the reaction mixture changes immediately after addition. The mixture was stirred under anhydrous conditions at room temperature for thirty hours, or till the completion of the reaction (monitored by t.l.c.). Solvents were removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (30:1) afforded the compound (CCXLVI) which was recrystallized from methanol (300 mg), m.p. 147°. ν_{\max} 1720 and 1250 cm^{-1} (conjugated carboethoxy group), 1710 (C_3 -oxo group), 1645 and 1585 cm^{-1} ($\text{C}=\text{C}$ of pyran); δ 4.25 q ($J=7$ Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$), 2.75 s (1H, $\text{C}_4\text{-H}$), 2.5 s (3H, $\text{C}=\text{C-CH}_3$) 2.2 br (2H, $\text{C}_2\text{-H}_2$), 1.36 t ($J=7$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$), 1.2 ($\text{C}_{10}\text{-Me}$), 0.73 ($\text{C}_{13}\text{-Me}$), 0.91 and 0.83 (other methyl protons); λ_{\max} 258 and 212 nm; M^+ 510 ($\text{C}_{33}\text{H}_{50}\text{O}_4$).

Analysis Found : C, 77.4 ; H, 9.7.

$\text{C}_{33}\text{H}_{50}\text{O}_4$ requires : C, 77.60; H, 9.86%.

Reaction of 4-cholesten-3-one (CCXVI) with ethylacetoacetate:
3 β -acetoxy-2'-methyl-3'-carboethoxycholestan[3 α ,5 α -de]-dihydro-
pyran (CCXLVIII)

A solution of the ketone (CCXVI)¹¹⁷ (1 g) in ethylacetoacetate (10 ml) was added to a well stirred solution of fused zinc chloride (1 g), acetic acid (10 ml) and acetic anhydride (10 ml). The reaction mixture was kept under anhydrous conditions at room temperature with continuous stirring for thirty hours. The solvents were removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (40:1) gave the dihydropyran (CCXLVIII) which was recrystallized from methanol (250 mg), m.p. 153°.

ν_{\max} 1735, 1260 ($\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$), 1720 ($\text{C}=\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-\text{CH}_2-\text{CH}_3-$), 1630 and 1555 cm^{-1} ($\text{C}=\text{C}$ bond of pyran); δ 4.23 q ($J=7$ Hz, 2H, $\text{CH}_3-\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$), 2.35 s (3H, $\text{CH}_3-\text{C}=\text{C}$), 2.0 s (3H, $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$), 1.3 t ($J=7$ Hz, 3H, $\text{CH}_3-\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$), 1.1, 0.9, 0.8 and 0.7 (other methyls); λ_{\max} 257 and 211 nm.

Analysis Found : C, 75.3 ; H, 9.9.

$\text{C}_{33}\text{H}_{56}\text{O}_5$ requires : C, 75.53; H, 10.07%.

Reaction of 6 β -bromo-4-cholesten-3-one (CCXVII) with ethylaceto-
acetate: 4,6-cholestadien-3-one (CCXLIV) and 2'-methyl-3'-carbo-
ethoxy-3-oxocholestan[7 α ,5 α -de]-6,7-dihydropyran (CCL)

A solution of the ketone (CCXVII)^{117a} (1.5 g) in ethylacetoacetate (15 ml) was added to a well stirred solution of fused zinc chloride (1.5 g) in acetic acid (15 ml) and acetic anhydride (15 ml). The reaction mixture was stirred under anhydrous conditions at room temperature for 20 hours. Removal of the solvent and usual work up provided an oil which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (35:1) afforded the ketone (CCXLIV) which was recrystallized from methanol (150 mg), m.p. and m.m.p. 79°. (lit.^{117b} m.p. 79-80°)

Further elution with light petroleum-ether (30:1) gave the dihydropyran (CCL) as a non-crystallizable oil (250 mg).

ν_{\max} 1720 (C=C-C(=O)-O-CH₂-CH₃), 1705 (C-C(=O)-C), 1580 (C=C) and 1260 cm⁻¹ (C-O stretching); δ 4.20 q (J=7 Hz, 2H, CH₃-CH₂-O-C(=O)-), 2.48 s (3H, C=C-CH₃), 2.2 br (4H, C₂-H₂ and C₄-H₂), 2.0 br (1H, C₇-allylic H), 1.32 t (J=7 Hz, 3H, CH₃-CH₂-O-C(=O)-), 1.2, 0.9, 0.8 and 0.63 (other methyls).

Analysis Found : C, 77.4 ; H, 10.1.

C₃₃H₅₂O₄ requires : C, 77.29; H, 10.22%.

4,6-Cholestadien-3-one (CCXLIV)

A mixture of 3-oxo-5,6 β -dibromo-5 α -cholestane (5 g), dimethylformamide (50 ml) and lithium chloride (1 g) was heated under reflux for one hour. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil (ca 4.5 g) which was chromatographed over silica gel (100 g). Elution with light petroleum-ether (35:1) gave the dienone (CCXLIV) which was recrystallized from methanol (2.5 g), m.p. and m.m.p. 79° (lit.^{117b} m.p. 79-80°).

Reaction of 4,6-cholestadien-3-one (CCXLIV) with ethylacetoacetate:
2'-methyl-3'-carboethoxy-3-oxocholestan[7 α ,5 α -de]-6,7-dihydropyran
(CCL)

The dienone (CCXLIV) (1 g) when allowed to react with ethylacetoacetate under similar conditions as described for the ketones (CCXIV), (CCXVI) and (CCXVII) afforded after usual work up and column chromatography a single compound (CCL) as a non-crystallizable oil (250 mg), which was identical to the sample of dihydropyran (CCL) obtained in earlier experiments.

Reaction of 4-cholesten-6-one (CCXII) with ethylacetoacetate:2'-methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydro-pyran (CCLIII)

A solution of the ketone (CCXII)¹⁰⁸ (1 g) in ethylacetoacetate (10 ml) was added to a well stirred solution of fused zinc chloride (1 g) in acetic acid (10 ml) and acetic anhydride (10 ml). The stirring was continued under anhydrous conditions at room temperature for 20 hours. After usual work up of the reaction mixture the residue was chromatographed over silica gel (30 g). Eluates from light petroleum-ether (30:1) gave the dihydropyran (CCLIII) which was recrystallized from methanol (200 mg), m.p. 120°.

ν_{\max} 1735, 1250 ($\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$), 1650 cm^{-1} (C=C); δ 5.78 s (1H, C₇-vinylic H), 4.15 q (J=7 Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$), 3.2 s (1H, C₃' α -methyne), 1.9 br (2H, C₃ and C₈-allylic protons), 1.3 t (J=7 Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-O-C(=O)-}$), 1.2, 1.1, 0.9, 0.8 and 0.63 (other methyls); λ_{\max} 252 and 210 nm; M^+ 496 ($\text{C}_{33}\text{H}_{52}\text{O}_3$).

Analysis Found : C, 79.66; H, 10.44.

$\text{C}_{33}\text{H}_{52}\text{O}_3$ requires : C, 79.78; H, 10.55%.

7-Oxo-5-cholesten-3 β -yl acetate (CCXLV)

A solution of t-butyl chromate, from t-butyl alcohol (60 ml), CrO_3 (20 g), acetic acid (84 ml) and acetic anhydride (10 ml), was added at 0° to a solution of 5-cholesten-3 β -yl acetate

(8 g) in carbontetrachloride (150 ml), acetic acid (30 ml) and acetic anhydride (10 ml). The contents were heated under reflux for three hours and then it was diluted with water. The organic layer was washed successively with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure furnished an oil which was crystallized from methanol to give the ketone (CCXLV) (4 g), m.p.156° (lit.¹³⁷ m.p.156-158°).

3,5-Cholestadien-7-one (CCIX)

To a solution of 7-oxo-5-cholesten-3 β -yl acetate (CCXLV) (5 g) in ethanol (100 ml) was added hydrochloric acid (5 ml; 12N) and the reaction mixture was heated under reflux for two hours. When allowed the reaction mixture to cool, the dienone (CCIX) separated as plates which was filtered and recrystallized from ethanol (3.5 g), m.p.116° (lit.¹²² m.p.118°).

Reaction of 3,5-cholestadien-7-one (CCIX) with ethylacetoacetate: 3 β -(1'-carboethoxypropan-2'-one)-5-cholesten-7-one (CCLVIII)

A solution of the dienone (CCIX) (1 g) in ethylacetoacetate (10 ml) was added to a well stirred solution of fused zinc chloride (1 g), acetic acid (10 ml) and acetic anhydride (10 ml). The stirring was continued under anhydrous conditions at room temperature for twenty hours. Removal of the solvent and usual

work up provided an oil which was chromatographed over silica gel (30 g). Eluates from light petroleum-ether (25:1) gave a single compound (CCLVIII) as a non-crystallizable oil (ca 200 mg).

ν_{\max} 1725, 1250 ($\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-O-CH}_2\text{-CH}_3$), 1710 (C=O), 1640 and 1620 cm^{-1} (C=C- $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ -); δ 5.91 s (1H, C₆-vinylic H), 4.25 q (J=7 Hz, carboethoxy methylene), 3.7 s (1H, 1'-methyne), 2.3 s (3H, CH₃CO), 1.2, 0.91, 0.83 and 0.7 (other methyls); λ_{\max} 238 nm.

Analysis Found : C, 79.96; H, 10.62.

C₃₃H₅₂O₃ requires : C, 79.78; H, 10.55%.

Reaction of 7-oxo-5-cholesten-3 β -yl acetate (CCXLV) with ethyl-acetoacetate

The ketone (CCXLV) (1 g) was allowed to react with ethyl-acetoacetate (10 ml) under conditions as described for earlier experiments. Usual work up and chromatography over silica gel (30 g) afforded the compound (CCLVIII) (100 mg) identical with the sample obtained earlier.

Reaction of 5-stigmastene (CCLX) with Mn(III) acetate in presence of acetic acid and acetic anhydride: 5 α -stigmastan-6 β -yl acetate (CCLXIV), 5 ξ ,6 ξ -dihydroxystigmastan-6 ξ -yl acetic acid γ -lactone (CCLXV) and 7 β -acetoxy-6 α -hydroxystigmastan-5 α -yl acetic acid γ -lactone (CCLXVI)

A mixture of 5-stigmastene (CCLX) (2.5 g), Mn(III) acetate (30 g), acetic acid (60 ml) and acetic anhydride (30 ml) was heated under reflux until the dark brown colour of Mn(III) ion disappeared (1.5 hour). The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil (ca 2.0 g) which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (20:1) gave (CCLXIV) as a non-crystallizable oil (200 mg). ν_{\max} 1735 and 1235 cm^{-1} (acetate); δ 4.43 br (1H, $W_{1/2}=4$ Hz, C_6 - αH ; equatorial), 1.2, 1.0, 0.9, 0.8 and 0.7 (methyl protons).

Analysis Found : C, 80.9 ; H, 11.6.

$\text{C}_{31}\text{H}_{54}\text{O}_2$ requires : C, 81.16; H, 11.86%.

Further elution with light petroleum-ether (15:1) gave (CCLXV) recrystallized from methanol (180 mg), m.p. 86° . ν_{\max} 3400 (OH), 1770 and 1220 cm^{-1} (γ -lactone); δ 2.33 br,s (2H, α -methylene of γ -lactone), 1.2, 1.1, 0.97, 0.90, 0.8 and 0.7 (methyl protons).

Analysis Found : C, 78.61; H, 10.81.

$C_{31}H_{52}O_3$ requires : C, 78.76; H, 11.08%.

Continued elution with light petroleum-ether (8:1) gave (CCLXVI) recrystallized from methanol (150 mg), m.p. 71° . γ_{\max}^{1780} (γ -lactone), 1735 and 1230 cm^{-1} (acetate); δ 5.7 br,d (1H, $C_6\beta$ -H; axial), 5.2 dd (1H, $C_7\alpha$ -H; axial), 2.4 br,s (2H, α -methylene of γ -lactone moiety), 2.0 s (3H, $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$), 1.1, 0.9, 0.8 and 0.7 (other methyls).

Analysis Found : C, 76.9 ; H, 10.2.

$C_{33}H_{53}O_4$ requires : C, 77.14; H, 10.39%.

Reaction of 5-stigmasten- 3β -yl chloride (CCLXI) with Mn(III) acetate in presence of acetic acid and acetic anhydride: 3β -chloro- 5α -stigmastan- 6β -yl acetate (CCLXXVIII) and 7α -acetoxy- 3α -hydroxy-stigmast-5-en- 4α -yl acetic acid γ -lactone (CCLXXIX)

A mixture of 5-stigmasten- 3β -yl chloride (CCLXI) (2 g), Mn(III) acetate (30 g), acetic acid (50 ml) and acetic anhydride (25 ml) was heated under reflux for two hours. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil (ca 1.7 g) which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (10:1) gave a non-crystallizable oil (CCLXXVIII)(300 mg). γ_{\max}^{1735} ,

1235 (acetate) and 760 cm^{-1} (C-Cl); δ 4.46 br, s ($W_{1/2}=4\text{ Hz}$, 1H, $C_6-\alpha H$; equatorial), 3.66 br ($W_{1/2}=16\text{ Hz}$, 1H, $C_3-\alpha H$), 2.0 s (3H, $CH_3-\overset{\overset{O}{\parallel}}{C}-$), 1.2, 1.06, 0.9, 0.8 and 0.7 (methyl protons). Positive Beilstein test.

Analysis Found : C, 75.3 ; H, 10.6.

$C_{31}H_{53}O_2Cl$ requires : C, 75.49; H, 10.83%.

Further elution with light petroleum-ether (5:1) gave (CCLXXIX) as a non-crystallizable oil (400 mg). ν_{\max} 1770 (γ -lactone), 1735, 1230 (acetate) and 1640 cm^{-1} (C=C); δ 6.65 d ($J=9\text{ Hz}$, 1H, C_6 -vinyllic H), 5.33 d ($J=9\text{ Hz}$, 1H, $C_7-\beta H$; pseudo-equatorial), 4.43 br ($W_{1/2}=5\text{ Hz}$, 1H, $C_3-\beta H$; pseudo-equatorial), 2.4 br (2H, methylene protons of γ -lactone), 2.0 s (3H, C_7 -acetate methyl protons), 1.1, 1.03, 0.9, 0.8 and 0.7 (other methyls). Beilstein test negative (chlorine absent).

Analysis Found : C, 77.2 ; H, 10.1.

$C_{33}H_{52}O_4$ requires : C, 77.30; H, 10.22%.

Reaction of 5-stigmasten-3 β -yl acetate (CCLXII) with Mn(III) acetate: 5 α -stigmastan-3 β ,6 β -yl diacetate (CCXC), 7 α -acetoxy-3 α -hydroxystigmast-5-en-4 α -yl acetic acid γ -lactone (CCLXXIX) and 7-oxo-5-stigmasten-3 β -yl acetate (CCXCI)

A mixture of 5-stigmasten-3 β -yl acetate (CCLXII) (2 g), Mn(III) acetate (20 g), acetic acid (50 ml) and acetic anhydride

(25 ml) was heated under reflux for one hour. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil, which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (12:1) gave (CCXC) as a non-crystallizable oil (300 mg). ν_{\max} 1735 br and 1230 cm^{-1} (acetate carbonyls at C_3 and C_6); δ 4.5 br, m (2H, $\text{C}_3\text{-H}$ and $\text{C}_6\text{-H}$), 2.05 s (6H, $2 \times \text{CH}_3\text{-C}(=\text{O})\text{-}$), 1.1, 1.01, 0.88, 0.7 and 0.6 (other methyls).

Analysis Found : C, 76.5 ; H, 10.7.

$\text{C}_{33}\text{H}_{56}\text{O}_4$ requires : C, 76.69; H, 10.92%.

Further elution with light petroleum-ether (8:1) gave (CCLXXIX) as non-crystallizable oil (350 mg) identical with the sample obtained earlier.

Continued elution with light petroleum-ether (6:1) gave (CCXCI) as solid compound, which was recrystallized from methanol (200 mg), m.p. and m.m.p. $168^{\circ}128$. ν_{\max} 1735, 1240 (C_3 -acetate) and 1670 cm^{-1} ($\text{C}=\text{C}-\text{C}=\text{O}$); δ 5.7 s (1H, C_6 -vinylic H), 4.8 br (W1/2=16 Hz, 1H, $\text{C}_3\text{-}\alpha\text{H}$; axial), 2.55 s (1H, $\text{C}_8\text{-H}$), 2.0 s (3H, $\text{CH}_3\text{-C}(=\text{O})\text{-}$), 1.1, 1.01, 0.9, 0.8 and 0.7 (methyl protons); λ_{\max} 238 nm.

5-Stigmasten-3 β -yl propionate (CCLXIII)

A mixture of β -sitosterol (50 g), pyridine (75 ml) and propionic anhydride (50 ml) was heated on a water bath for two hours. The reaction mixture was poured into ice cooled water, and the solid thus obtained was filtered under suction, washed with water and air dried. Recrystallization of the crude product from acetone gave 5-stigmasten-3 β -yl propionate (CCLXIII) (45 g), m.p. 117°. ν_{\max} 1735 and 1220 cm^{-1} ($\text{CH}_3\text{-CH}_2\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-O-}$); δ 5.33 br (1H, C₆-vinylic H), 4.46 br (W1/2=16 Hz, 1H, C₃- α H), 2.2 q (J=7 Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-}$), 1.2, 1.1, 1.0, 0.9, 0.8 and 0.7 (methyl protons).

Reaction of 5-stigmasten-3 β -yl propionate (CCLXIII) with Mn(III) acetate: 6 β -acetoxy-5 α -stigmastan-3 β -yl propionate (CCXCII), 3 β -propionoxy-5 β -hydroxystigmastan-6 α -yl acetic acid γ -lactone (CCXCIII) and 4 β -hydroxystigmast-5-en-3 β -yl acetic acid γ -lactone (CCXCIV)

5-Stigmasten-3 β -yl propionate (CCLXIII) (2.5 g) with Mn(III) acetate (30 g), acetic acid (60 ml) and acetic anhydride (30 ml) was heated under reflux for two hours. The reaction mixture was poured into cold water and extracted with ether. Usual work up and removal of the solvent gave an oil which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (20:1) gave (CCXCII) as an oil (200 mg). ν_{\max} 1735 and 1230 cm^{-1} (acetate

and propionate carbonyls); δ 4.55 br (1H, C₃- α H; axial) and 4.55 tall (1H, C₆- $\underline{\text{H}}$; equatorial), 2.1 q (J=7 Hz, 2H, CH₃-CH₂- $\overset{\text{O}}{\parallel}\text{C}$ -O-), 2.0 s (3H, -C=C-CH₃), 1.2, 1.1, 0.9, 0.8 and 0.6 (other methyls).

Analysis Found : C, 76.8; H, 10.9.

C₃₄H₅₈O₄ requires : C, 76.93; H, 11.01%.

Further elution with light petroleum-ether (16:1) gave the lactone (CCXCIII) recrystallized from methanol (200 mg), m.p. 176°. ν_{max} 1765 (γ -lactone), 1725 and 1235 cm⁻¹ (3 β -propionate); δ 4.85 br (W1/2=6 Hz, 1H, C₃- α H; equatorial), 2.3 br, s (2H, -CH₂-C=O), 2.3 q (2H, CH₃-CH₂- $\overset{\text{O}}{\parallel}\text{C}$ -O-), 1.2, 1.16, 1.0, 0.8 and 0.7 (methyl protons); M⁺• 528 (C₃₄H₅₆O₄).

Analysis Found : C, 77.1 ; H, 10.5.

C₃₄H₅₆O₄ requires : C, 77.22; H, 10.67%.

Continued elution with light petroleum-ether (8:1) gave the other lactone (CCXCIV) recrystallized from methanol (250 mg), m.p. 95°. ν_{max} 1775 (γ -lactone), 1650 (C=C) and 1230 cm⁻¹ (C-O); δ 6.05 m (1H, C₆-vinylic $\underline{\text{H}}$), 5.33 d (J=8 Hz, 1H, C₄- α H; pseudo-equatorial), 2.43 br (2H, γ -lactone methylene), 1.2, 1.06, 0.9, 0.8 and 0.7 (methyl protons).

Analysis Found : C, 81.8 ; H, 10.9.

C₃₁H₅₀O₂ requires : C, 81.93; H, 11.01%.

PART - IV

The mass spectra were measured on AEI MS-9 mass spectrometer at 70 eV using direct insertion sample inlet system at a source temperature of about 200°C. The accurate mass measurements were related to fragment ions of heptacosafuorotributylamine at a resolving power of 15,000.

The value m/z of the fragment ions from various compounds are tabulated below. The values in parentheses are the relative abundance (%) of the peaks with respect to base peak taken as 100%, and the composition of fragment ions as determined by accurate mass measurement.

2'-Phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXI)

M^+ 472 (88.8; $C_{33}H_{48}N_2$), 471 (22.2), 458 (9.1), 457 (100; $C_{32}H_{45}N_2$), 456 (8.1), 388 (4.1), 387 (9.9), 386 (5.1), 360 (3.9), 359 (10.2), 358 (4.1), 345 (3.9), 344 (2.9), 343 (3.1), 332 (5.2), 331 (4.8), 319 (3.5), 318 (5.2), 317 (4.3), 304 (2.2), 303 (3.9), 302 (2.5), 264 (3.7), 263 (7.2; $C_{18}H_{19}N_2$), 262 (3.1), 261 (3.7), 249 (7.1; $C_{17}H_{17}N_2$), 248 (4.2), 247 (8.8), 237 (6.2), 236 (2.2), 235 (4.1), 225 (22.5; $C_{15}H_{17}N_2$), 224 (54.8; $C_{15}H_{16}N_2$), 223 (19.1), 212 (4.1), 211 (14.2; $C_{14}H_{15}N_2$), 210 (4.9; $C_{14}H_{14}N_2$),

209 (4.2), 197 (4.1), 196 (4.2), 195 (4.9), 148 (3.2), 147 (4.3), 146 (3.1), 133 (3.8), 132 (3.3), 131 (3.3), 130 (6.5), 107 (4.2), 106 (3.2), 105 (20.2), 95 (11.3), 93 (9.9), 91 (8.4), 81 (8.8), 80 (17.2), 79 (8.9), 77 (19.3), 57 (22.0) and 55 (22.3).

2'-Phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXL)

M^+ 500 (50.2; $C_{35}H_{52}N_2$), 499 (12.6), 485 (100; $C_{34}H_{49}N_2$), 484 (5.2), 416 (5.1), 415 (6.3), 360 (6.1), 358 (8.4), 345 (14.9), 344 (10.2), 343 (6.2), 332 (5.5), 331 (7.2), 330 (4.5), 318 (5.2), 317 (11.9), 304 (6.4), 303 (16.1), 302 (7.2), 276 (7.6), 275 (13.2), 274 (6.2), 263 (29.3; $C_{18}H_{19}N_2$), 262 (6.9), 261 (16.5), 249 (27.2; $C_{17}H_{17}N_2$), 248 (12.2), 225 (26.9), 224 (55.4; $C_{15}H_{16}N_2$), 211 (43.1; $C_{14}H_{15}N_2$), 210 (25.0; $C_{14}H_{14}N_2$), 209 (22.1), 196 (16.5), 195 (21.2), 148 (21.6), 147 (26.2), 146 (4.9), 134 (17.9), 133 (32.1), 132 (13.9), 123 (55.1), 122 (71.0), 121 (48.2), 107 (41.5), 105 (44.2), 95 (78.9), 91 (83.9), 81 (76.2), 79 (91.5), 77 (73.3), 69 (80.0), 67 (68.1), 57 (52.5) and 55 (52.7).

2'-Phenyl-2,4-cholestadieno[4,6-cd]-pyrazole (CCXXXIII)

M^+ 470 (30.4; $C_{33}H_{46}N_2$), 469 (19.2), 455 (100; $C_{32}H_{43}N_2$), 454 (11.9), 358 (2.2), 357 (4.6), 356 (2.7), 343 (3.0), 342 (3.1), 329 (2.9), 328 (2.9), 317 (2.0), 316 (2.9), 315 (3.1), 301 (6.1),

300 (3.7), 262 (2.0), 261 (6.9; $C_{18}H_{17}N_2$), 260 (3.5), 248 (3.9),
 247 (10.2; $C_{17}H_{15}N_2$), 246 (5.8), 223 (19.9), 222 (44.9; $C_{15}H_{14}N_2$),
 221 (3.3), 209 (16.1; $C_{14}H_{13}N_2$), 208 (20.3), 207 (40.1), 206
 (10.9), 194 (4.0), 193 (8.3), 192 (2.5), 146 (3.2), 145 (8.1), 131
 (8.0), 130 (3.9), 119 (8.1), 117 (16.3), 109 (10.0), 107 (14.1),
 105 (17.6), 95 (20.1), 93 (26.1), 91 (19.0), 77 (36.0), 71 (31.9),
 69 (35.1), 57 (16.0), 55 (75.5), 51 (14.1) and 50 (3.9).

3-Oxo-2'-phenyl-4-cholesteno[4,6-cd]-pyrazole (CCXXV)

M^+ 486 (100, $C_{33}H_{46}N_2O$), 472 (10.1), 471 (21.2; $C_{32}H_{43}N_2O$),
 458 (9.9), 457 (2.2), 444 (2.6), 443 (4.0), 430 (2.1), 429 (2.2),
 402 (2.2), 401 (3.9), 374 (3.2), 373 (11.9), 360 (4.0), 359 (13.8),
 358 (2.2), 346 (4.9), 345 (9.1), 344 (1.9), 332 (4.0), 331 (9.3),
 318 (3.5), 317 (7.7), 305 (4.1), 303 (4.1), 277 (4.6; $C_{18}H_{17}N_2O$),
 276 (2.2), 263 (13.2; $C_{17}H_{15}N_2O$), 262 (2.9), 261 (15.1), 250 (5.0),
 249 (14.5), 239 (32.1), 238 (69.9; $C_{15}H_{14}N_2O$), 237 (10.1), 225
 (14.3; $C_{14}H_{13}N_2O$), 224 (4.8), 223 (8.1), 210 (5.0), 209 (12.2), 208
 (3.2), 197 (6.1), 196 (7.0), 195 (8.2), 183 (3.9), 182 (4.7), 171
 (2.6), 170 (5.2), 169 (3.9), 157 (4.2), 156 (4.9), 133 (4.2), 131

(4.1), 130 (4.9), 118 (3.5), 117 (4.2), 95 (6.3), 93 (6.9), 91 (6.9), 77 (18.2), 71 (14.1), 69 (14.3), 67 (9.1), 57 (32.8) and 55 (28.2).

3-Oxo-2'-phenyl-4-stigmasteno[4,6-cd]-pyrazole (CCXLII)

M^+ 514 (39.1; $C_{35}H_{50}N_2O$), 500 (36.5), 499 (100; $C_{34}H_{47}N_2O$), 498 (39.7), 487 (6.1), 486 (21.8), 472 (6.1), 471 (8.0), 429 (3.9), 402 (2.1), 401 (6.2), 374 (3.1), 373 (7.9), 372 (2.2), 360 (2.8), 359 (11.9), 347 (1.7), 346 (3.9), 345 (7.2), 332 (6.1), 331 (8.0), 318 (2.8), 317 (6.4), 316 (1.9), 290 (2.5), 289 (4.3), 278 (2.9), 277 (6.4; $C_{18}H_{17}N_2O$), 264 (4.1), 263 (10.1; $C_{17}H_{15}N_2O$), 262 (4.2), 261 (12.2), 250 (3.4), 249 (11.2), 239 (26.2), 238 (58.8; $C_{15}H_{14}N_2O$), 237 (8.6), 225 (12.1; $C_{14}H_{13}N_2O$), 224 (5.1), 223 (6.2), 210 (6.5), 209 (11.1), 197 (2.6), 196 (6.0), 195 (7.5), 183 (4.1), 182 (4.2), 170 (4.2), 169 (3.9), 158 (1.9), 157 (4.3), 97 (5.1), 95 (5.9), 93 (7.9), 91 (8.3), 83 (6.9), 81 (7.5), 79 (6.2), 78 (6.2), 77 (14.1), 71 (14.2), 69 (16.4), 57 (27.8), 55 (29.9) and 43 (55.8).

2'-Phenyl-4-cholesteno[4,6-cd]-pyrazole-3-one phenylhydrazone (CCXXXVII)

M^+ 576 (100; $C_{39}H_{52}N_4$), 562 (2.9), 561 (5.2), 560 (3.2), 486 (2.8), 485 (11.9), 484 (25.1; $C_{33}H_{46}N_3$), 470 (2.6), 469 (4.2),

330 (3.8), 329 (2.3), 263 (1.3), 262, 261 (4.2; $C_{17}H_{15}N_3$), 260 (2.3), 249 (1.2), 248 (2.2), 247 (3.8), 246 (1.8), 245 (1.8), 238 (1.9), 237 (5.1), 236 (3.9; $C_{15}H_{14}N_3$), 235 (1.8), 223 (4.5), 223 (4.5; $C_{14}H_{13}N_3$), 222 (3.9), 221 (2.1), 220 (1.1), 209 (2.1), 208 (3.2), 207 (4.7), 206 (2.8), 196 (1.9), 195 (2.9), 194 (1.8), 167 (3.9), 166 (3.8), 165 (2.7), 150 (1.7), 149 (5.1), 148 (2.1), 119 (4.8), 118 (3.0), 106 (1.8), 105 (6.2), 104 (2.9), 95 (15.2), 94 (10.2), 93 (10.2), 85 (5.0), 83 (6.9), 77 (12.2), 71 (7.9) and 69 (9.9).

6-Oxo-5 α -3-cholesteno[3,4]-N,N-phenylhydrazine (CCXXXV)

M^+ 488 (40.1; $C_{33}H_{48}N_2O$), 487 (100; $C_{33}H_{47}N_2O$), 474 (2.3), 473 (5.9), 472 (4.2), 471 (1.9), 460 (8.2; $C_{32}H_{48}N_2$), 459 (24.2), 445 (4.1), 444 (5.9), 417 (4.0), 416 (5.9), 402 (4.1), 401 (4.2), 400 (8.2), 300 (4.5), 246 (4.3), 245 (5.8), 211 (7.9), 210 (6.4), 200 (3.9), 199 (8.1), 198 (36.7; $C_{13}H_{14}N_2$), 197 (48.2; $C_{13}H_{13}N_2$), 196 (12.5), 184 (6.2), 183 (6.8), 182 (8.5), 181 (3.9), 170 (3.2), 169 (7.6), 168 (11.4), 167 (3.6), 159 (6.2), 158 (2.9), 155 (4.3), 154 (4.6), 144 (4.2), 143 (6.2), 130 (4.8), 109 (6.1), 107 (5.9), 97 (8.1), 95 (9.9), 93 (6.1), 81 (11.9), 79 (8.2), 71 (8.4), 69 (12.2), 67 (10.1), 57 (19.9) and 55 (24.2).

2'-Methyl-3'-carboethoxy-3-oxo-5-cholesteno[4 α ,6-de]- γ -pyran(CCXLVI)

M^+ 510 (100; $C_{33}H_{50}O_4$), 496 (2.2), 495 (7.8; $C_{32}H_{47}O_4$), 467 (6.9), 466 (20.0), 465 (37.2; $C_{31}H_{45}O_3$), 451 (5.1), 450 (12.7), 438 (5.2), 437 (12.9; $C_{30}H_{45}O_2$), 423 (2.1), 422 (7.9), 370 (2.4), 369 (7.9), 368 (25.2; $C_{26}H_{40}O$), 353 (4.9), 351 (5.1), 261 (2.2), 260 (6.5), 255 (6.1), 206 (5.2), 205 (12.8), 204 (7.6), 181 (20.1), 180 (89.9; $C_{10}H_{12}O_3$), 136 (10.1), 135 (22.6), 122 (5.2), 121 (16.2), 120 (5.3), 107 (20.1), 106 (16.3), 104 (25.2), 95 (22.4), 93 (17.1), 91 (15.1), 82 (5.1), 81 (30.2), 71 (24.9), 69 (30.2), 57 (50.1), 55 (42.1), 44 (60.1) and 43 (100).

2'-Methyl-3'-carboethoxy-4,6-cholestadieno[4,6-de]-2',3'-dihydro-pyran (CCLIII)

M^+ 496 (60.1; $C_{33}H_{52}O_3$), 482 (7.5), 481 (20.1; $C_{32}H_{49}O_3$), 453 (5.2), 451 (50.4), 450 (4.9), 436 (2.4), 435 (7.4), 425 (37.6), 423 (100; $C_{30}H_{47}O$), 409 (3.6), 408 (10.2), 407 (3.8), 384 (2.6), 383 (3.9), 382 (2.2), 356 (2.8), 355 (3.2), 354 (1.9), 342 (2.1), 341 (5.1), 296 (2.9), 295 (3.2), 294 (5.8), 284 (4.2), 283 (12.3), 282 (2.9), 270 (3.2), 269 (10.1), 241 (4.1), 239 (3.9), 199 (8.9), 197 (6.3), 189 (5.9), 187 (8.2), 175 (10.2), 173 (5.1), 171 (4.5), 161 (15.1), 160 (6.9), 159 (7.2), 149 (5.5), 148 (4.2), 147 (11.6), 146 (3.2), 145 (7.9), 135 (9.1), 134 (5.2), 133 (15.4), 120 (10.4), 119 (4.9), 118 (7.5), 108 (11.9), 106 (9.5), 104 (13.6), 95 (21.9),

93 (11.4), 91 (14.9), 86 (14.5), 84 (16.8), 82 (25.2), 71 (26.9), 69 (30.1), 57 (50.1), 55 (4.2) and 43 (52.9).

3 β -Propionyxy-5 β -hydroxystigmastan-6 α -yl acetic acid γ -lactone

(CCXCIII)

M^+ 528 (6.3; $C_{34}H_{56}O_4$), 469 (2.3), 468 (6.2), 455 (20.7), 454 (74.8; $C_{31}H_{50}O_2$), 440 (11.8), 439 (46.9), 413 (14.9), 412 (11.8), 411 (6.1), 410 (9.8), 401 (6.9), 400 (46.8; $C_{27}H_{44}O_2$), 399 (11.9), 395 (7.1), 394 (7.9), 314 (7.0), 313 (24.9; $C_{21}H_{29}O_2$), 312 (5.2), 287 (10.1), 286 (18.1), 285 (7.2), 273 (14.9), 272 (35.2; $C_{18}H_{24}O_2$), 271 (50.2), 258 (4.9), 257 (7.9), 228 (2.8), 227 (9.9), 226 (7.2), 219 (4.2), 218 (10.2), 217 (8.5), 213 (12.4), 212 (10.2), 211 (15.2), 204 (5.1), 203 (12.3), 202 (5.1), 191 (10.3), 189 (11.9), 167 (30.2), 166 (25.4), 165 (20.0), 149 (23.5), 147 (22.9), 145 (20.2), 134 (21.7), 133 (22.4), 130 (14.9), 123 (25.2), 121 (28.3), 119 (34.3), 109 (32.2), 107 (40.3), 105 (36.5), 95 (50.2), 93 (37.6), 91 (24.5), 85 (26.3), 83 (31.7), 81 (75.7), 71 (37.8), 69 (51.4), 67 (33.4), 57 (96.6), 55 (75.5), 43 (100) and 41 (42.2).

7 α -Acetoxy-3 α -hydroxystigmast-5-en-4 α -yl acetic acid γ -lactone

(CCLXXIX)

m/z 452 (11.6; $C_{31}H_{48}O_2$), 438 (3.1), 437 (9.3), 436 (2.9), 411 (4.8), 410 (6.3), 409 (3.1), 408 (6.2), 397 (4.9), 396 (11.3), 393 (5.1), 392 (12.5), 311 (6.9), 310 (3.6), 309 (3.5), 271 (3.1),

270 (6.2), 269 (9.4), 265 (5.9), 264 (3.2), 256 (1.8), 255 (5.4),
254 (1.8), 225 (4.5), 224 (3.6), 223 (3.6), 213 (4.9), 212 (4.8),
211 (7.8), 199 (6.2), 198 (3.2), 197 (4.4), 187 (6.3), 186 (3.2),
185 (7.8), 184 (3.2), 183 (5.9), 173 (10.8), 171 (11.2), 167
(10.1), 166 (6.9), 165 (7.9), 164 (9.2), 162 (4.8), 161 (10.8), 159
(40.8), 158 (12.2), 157 (21.1), 149 (16.9), 147 (18.1), 145 (23.9),
143 (15.2), 135 (15.5), 133 (19.9), 131 (16.2), 123 (17.8), 121
(22.2), 119 (24.8), 109 (29.5), 107 (35.2), 105 (35.1), 95 (49.2),
93 (35.3), 91 (35.2), 85 (22.9), 83 (24.2), 81 (87.8), 71 (51.5),
69 (64.4), 67 (54.5), 57 (84.4), 55 (100) and 43 (97.8).

REFERENCES

1. L. Knorr, Ger. Pat., 26, 429 (1883) [Friedlander, 1, 208].
2. L. Knorr, Ber., 16, 2597 (1883).
3. L. Knorr, Ber., 17, 546 & 2032 (1884).
4. L. Knorr and A. Blank, Ber., 18, 311 (1885).
5. K.V. Auwers and Schmidt, Ber., 58, 528 (1925).
6. K.V. Auwers and H. Mauss, Ann., 452, 182 (1927).
7. Panizzi, Gazz. Chim. ital., 77, 283 (1947).
8. Buchner, Ann., 273, 214 (1893).
9. Viguiier, Ann. Chim., 28[8], 433 (1913).
10. Andre, Ann. Chim., 29[8], 540 (1913).
11. K. Bowden, E.A. Braude, E.R.H. Jones and B.C.L. Weeden, J. Chem. Soc., 45 (1946).
12. K.V. Auwers and Ottens, Ber., 58, 2072 (1925).
13. K.V. Auwers and Kreuder, Ber., 58, 1974 (1925).
14. Wegscheider and Spath, Monatsh., 31, 997 (1910).
15. L.C. Raiford and H.L. Davis, J. Am. Chem. Soc., 50, 156 (1928).
16. L.C. Raiford and W.J. Peterson, J. Org. Chem., 1, 544 (1936).
17. L.C. Raiford and Entrikin, J. Am. Chem. Soc., 55, 1125 (1933).
18. L.C. Raiford and R.H. Manley, J. Org. Chem., 5, 590 (1940).
19. L.C. Raiford and L.K. Tanzer, J. Org. Chem., 6, 722 (1941).
20. K.V. Auwers and H. Mauss, Ber., 59, 611 (1926).
21. Laubmann, Ber., 21, 1212 (1888).
22. K.V. Auwers and Muller, Ber., 41, 4230 (1908).
23. Kohler, Am. Chem. J., 42, 375 (1909).

24. Buchner and Perkel, Ber., 36, 3774 (1903).
25. L. Knorr, Ber., 20, 1096 (1887).
26. Parham and Hasek, J. Am. Chem. Soc., 76, 799 & 935 (1954).
27. H.M. Mokhtar and J. Wajtanis, Ind. J. Chem., 24B(2), 188 (1985).
28. M.G. Joshi and K.N. Wadodkar, Ind. J. Chem., 20B(12), 1089 (1981).
29. H.A. Hammouda and S.M. Hussain, Ind. J. Chem., 24B(6), 632 (1985).
30. B.H. Nicolet, J. Am. Chem. Soc., 57, 1098 (1935).
31. L. Knorr and Liebig's, Ann., 238, 200 (1887).
32. T. Lorand, D. Szabo, A. Foldesi, L. Parkanyi, A. Kalman and A. Neszmelyi, J. Chem. Soc., Perkin Trans. I, (3), 481 (1985).
33. L. Ruzicka and P.A. Plattner, Helv. Chim. Acta, 21, 1717 (1938).
34. R.O. Clinton, A.J. Manson, F.W. Stonner, A.L. Beyler, G.O. Potts and A. Arnold, J. Am. Chem. Soc., 81, 1513 (1959).
35. H.A. Burke, Jr., and G.W. Liddle, Abstr. Endocrine Society Meeting, Atlantic City, N.J. 45 (1959).
36. R.O. Clinton, A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, W.B. Dickinson and C. Carabateas, J. Am. Chem. Soc., 83, 1478 (1961).
37. W.R. Benn and R.M. Dodson, J. Org. Chem., 29, 1142 (1964).
38. R. Hirschmann, P. Buchschacher, N.G. Steinberg, J.H. Fried, R. Ellis, G.J. Kent and M. Tishler, J. Am. Chem. Soc., 86, 1520 (1964).
39. R.O. Clinton, A.J. Manson, F.W. Stonner, R.G. Christiansen, A.L. Beyler, G.O. Potts and A. Arnold, J. Org. Chem., 26, 279 (1961).

54. Meerwein and Vossen, J. Pr. Chem., 141, 149 (1934).
55. W.C. Dovey and R. Robinson, J. Chem. Soc., 1389 (1935).
56. Paul, Bull. Soc. Chim. France, (a) [4]53, 1489 (1933);
(b) [5]1, 971 (1934); (c) [5]2, 311, 2220 (1935).
- 57a. C.H. Kline Jr. and J. Turkevich, J. Am. Chem. Soc., 67, 498 (1945).
b. L.E. Schniepp and H.H. Geller, J. Am. Chem. Soc., 68, 1646 (1946).
58. Sawyer and Andrus, Org. Syntheses, 23, 25 (1943).
59. G.F. Woods and D.N. Kramer, J. Am. Chem. Soc., 69, 2246 (1947).
60. Merling, Chem. Zentr., II, 1421 (1910).
61. Delepine, Compt. rend., 150, 394, 535 (1910).
62. Delepine and Horeau, Bull. Soc. Chim. France, [5]5, 339 (1938).
63. R.G. Fargher and W.H. Perkin Jun., J. Chem. Soc. Transactions, 105, 1353 (1914).
64. J. Wolinsky and M.A. Tyrell, Chim. Ind.(London), 1104 (1960).
65. P. Barbier, C.R. Acad. Sci. Paris, 127, 870 (1898).
66. L.G. Jupp, G.A.R. Kon and E.H. Lockton, J. Chem. Soc., 1639 (1928).
67. Y.L. Chow, Tet. Lett., 1337 (1964).
68. J. Wolinsky and H.S. Hauer, J. Org. Chem., 34, 380 (1969).
69. K. Sheth, E. Ramstad and J. Wolinsky, Tet. Lett., 394 (1961).
70. C. Djerassi, T. Nakano, A.N. James, L.H. Zalkow, E.J. Eisenbraun and J.H. Shoolery, J. Org. Chem., 26, 1192 (1961).
71. J. Wolinsky and H.S. Hauer, J. Org. Chem., 34, 3169 (1969).

72. P. Schenone, F. Evangelisti, G. Bignardi and A. Bargagna, *Ann. Chim. (Rome)*, **64** (9-10), 613 (1974) [CA: 84, 121596s (1976)].
73. T.A. Gosink, *J. Org. Chem.*, **39**, 1942 (1974).
74. R.W. Saalfrank, *Tet. Lett.*, 4509 (1974).
75. P. Schiess and H.L. Chia, *Helv. Chim. Acta*, **53**, 485 (1970).
76. A. Duperrier and J. Dreux, *Tet. Lett.*, 3127 (1970).
77. G-Fodor and Chen-Pet Hsiung, *Liebigs Ann. Chem.*, 1742 (1974).
78. Ae. de Groot and B.J.M. Jansen, *Tet. Lett.*, 3707 (1975).
79. G. Jenner, H. Abdi-Oskoui and J. Rimmelin, *Bull. Soc. Chim. France*, (9-10, Pt. 2), 983 (Fr.) (1977) [CA: 88, 169885v, 1978)].
80. J.H. Pardanani and S. Sethna, *J. Ind. Chem. Soc.*, **55**, 806 (1978).
81. J.H. Pardanani, Y.G. Gaekwad and S. Sethna, *J. Ind. Chem. Soc.*, **56**, 644 (1979).
82. L.V. Vlasova, T.I. Tyrina, S.K. Klimenko and V.G. Kharchenko, *Khim. Geterotsikl. Soedin.*, (4), 470 (1979) (CA: 91, 91447u (1979)].
83. D. Dvorak and Z. Arnold, *Tet. Lett.*, 4401 (1982).
84. J.L. Soto, C. Seoane, N. Martin and M. Quinteiro, *Heterocycles*, **22(1)**, 01 (1986).
85. B. Green, R.I. Crane, I.S. Khaidem, R.S. Leighton, S.S. Newaz and T.E. Smyser, *J. Org. Chem.*, **50**, 640 (1985).
86. S. Coffey 'Rodd's Chemistry of Carbon Compounds', **1**, Part D, Elsevier Publishing Company, New York, 99 (1965).
87. Y. Asahina and A. Fujita, *Actaphytochim. Japan*, **1**, 01 (1922).
88. H. Baer, M. Holden and B.C. Seegal, *J. Biol. Chem.*, **162**, 65 (1946).

89. L.J. Haynes and E.R.H. Jones, J. Chem. Soc., 954 (1946).
90. J.C. Mitchell and G. Dupuis, Brit. J. Dermatol., 84(2), 139 (1971).
91. L. Sequeira, S.M. Kupchan and R.J. Hemingway, Science, 161, 789 (1968).
92. S.M. Kupchan, J.E. Kelsey, M. Maruyama, J.M. Cassady, J.C. Hemingway and J.R. Knox, J. Org. Chem., 34, 3876 (1969).
93. R. Criegee, 'Oxidation in Organic Chemistry', A.K.B. Wilberg, Ed., Academic Press, New York, 277 (1965).
94. E.I. Heiba, R.M. Dessau and W.J. Koehl, Jr., J. Am. Chem. Soc., 90, 5905 (1968).
95. O.T. Christiansen, Z. Anorg. Allgem. Chem., 27, 325 (1901).
96. E.I. Heiba, R.M. Dessau and W.J. Koehl, J. Am. Chem. Soc., 90, 2706 (1968).
97. J.B. Bush, Jr. and H. Finkbeiner, J. Am. Chem. Soc., 90, 5903 (1968).
98. E.I. Heiba, R.M. Dessau and P.G. Rodewald, J. Am. Chem. Soc., 96, 7977 (1974).
99. E.I. Heiba, R.M. Dessau and W.J. Koehl, J. Am. Chem. Soc., 91, 138 (1969).
100. R.E. Vander Ploeg, R.W. Dekorte and E.C. Kooyaman, J. Catal., 10, 52 (1968).
101. M. Okano, Bull. Chem. Soc. Japan, 49, 1041 (1976).
102. K. Oishi and K. Kurosawa, Bull. Chem. Soc. Japan, 53, 179 (1980).
103. K. Kurosawa and T. Tsujita, Bull. Chem. Soc. Japan, 54, 2391 (1981).
104. H. Nishino, Bull. Chem. Soc. Japan, 58, 217 (1985).

105. W.E. Fristad and J.R. Peterson, J. Org. Chem., 50, 10 (1985).
106. W.E. Fristad and S.S. Hershberger, J. Org. Chem., 50, 1026 (1985).
107. M.S. Ahmad, S.Z. Ahmad and I.A. Ansari, J. Chem. Research(S), 374 (1984).
108. H. Reich, F.E. Walker and R.W. Collins, J. Org. Chem., 16, 1753 (1951).
109. L.J. Bellamy, 'The Infrared Spectra of Complex Molecules' (Methuen London), 1958.
110. T.W. Milligan and B.C. Minor, J. Org. Chem., 27, 4663 (1962).
111. E.F. Pratt and T.P. McGovern, J. Org. Chem., 29, 1540 (1964).
112. I. Bhatnagar and M.V. George, J. Org. Chem., 32, 2252 (1967).
113. W.A.F. Gladstone and R.O.C. Norman, J. Chem. Soc.(C), 1536 (1966).
114. I.M. Heilbron, E.R.H. Jones and F.S. Spring, J. Chem. Soc., 801 (1937).
115. R. O'Connor and W. Rosenbrook, Jr., J. Org. Chem., 26, 2508 (1961).
116. A.H. Milburn, E.V. Truter and W.P. Woodford, J. Chem. Soc., 1740 (1956).
117. L.F. Fieser, J. Am. Chem. Soc., 75, 5421 (1953).
 - (a) L. Ruzicka, W. Bosshard, W.H. Fischer and H. Wirz, Helv. Chim. Acta, 19[2], 1147 (1936).
 - (b) L.D. Antonaccio, L.M.F. Serpa, W. Wanderley and F.F. Wanda, An. Acad. Brasil. Ciene., 44, 419 (1972). [CA: 79, 137368b, 1973].
118. J.G. Schantl, P. Karpellus and M. Preat, Tetrahedron, 38, 2643 (1982).

119. R. O'Connor, J. Org. Chem., 26, 4375 (1961).
120. K.A. Kumar and G. Srimannarayana, Ind. J. Chem., 23B[10], 969 (1984).
121. I.R. absorption spectroscopy by Koji Nakanishi, Holden-Day, Inc. San Fransisco, 52 (1962).
122. Q.R. Petersen and C.T. Chen, J. Am. Chem. Soc., 77, 2557 (1955).
123. P. Wailes, M.C. Whiting and L. Fowden, Nature(London), 174, 130 (1954).
124. S.M. Kupchan, M.A. Eakin and A.M. Thomas, J. Med. Chem., 14(2), 1147 (1971).
125. S.M. Kupchan, Y. Aynehchi, S.M. Cassady, H.K. Schnoes and A.L. Burlingame, J. Org. Chem., 34, 3867 (1969).
126. S.Z. Ahmad, Ph.D. Thesis, A.M.U. Aligarh, (1986).
127. N.S. Bhacca and D.H. Williams 'Application of NMR Spectroscopy in Organic Chemistry', Holden-Day, Inc. San Fransisco, 79 (1964).
128. I.A. Ansari, Ph.D. Thesis, A.M.U. Aligarh, (1983).
129. R.H. Baker and E.N. Squire, J. Am. Chem. Soc., 70, 1487 (1948).
130. C.E. Anagnostopoulos and L.F. Fieser, J. Am. Chem. Soc., 76, 532 (1954).
131. J.R. Bull, E.R.H. Jones and G.D. Meakins, J. Chem. Soc., 2601 (1965).
132. C.W. Shoppee, R.H. Jenkins and G.H.R. Summers, J. Chem. Soc., 1657 (1958).
133. H.B. Henbest and T.I. Wrigly, J. Chem. Soc., 4596 (1957).
134. L.F. Fieser and M. Fieser, 'Steroids' Reinhold Publishing Corporation, New York, 28 (1959).

135. R.M. Dodson and B. Riegel, J. Org. Chem., 13, 424 (1948).
136. L.F. Fieser and S. Rajagopalan, J. Am. Chem. Soc., 71, 3938 (1949).
137. L.F. Fieser, M. Fieser and R.N. Chakravarti, J. Am. Chem. Soc., 71, 226 (1949).

Reaction of Phenylhydrazine with α,β -Unsaturated Steroidal Ketones: Synthesis of Steroidal Pyrazoles

M S AHMAD*, SHAMIM A ANSARI & S MASARRAT ALI

Department of Chemistry, Aligarh Muslim University, Aligarh 202001

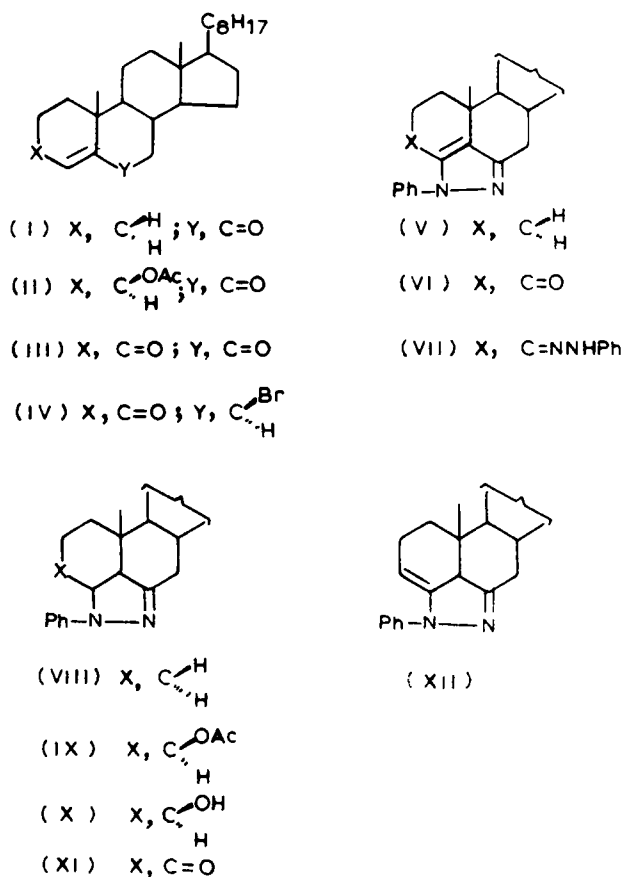
Received 5 December 1983, accepted 2 January 1985

Reaction of 4-cholesten-6-one (I) with phenylhydrazine in the presence of acetic acid gives 2-phenyl-4-cholesten-3-one (II) whereas 6-oxo-4-cholesten-3 β -yl acetate (III) and 4-cholestene-3,6-dione (IV) afford the same pyrazole, 3-oxo-2'-phenyl-4-cholesten-3-one (V). 6 β -Bromo-4-cholesten-3-one (VI) gives besides the pyrazole VI, 2-phenyl-4-cholesten-3-one (VII) which is also obtained by treating VI with phenylhydrazine. The structures are supported mainly by their spectral behaviour and chemical properties. Probable pathways for their formation have also been suggested.

Pyrazoles can be conveniently obtained by the reaction of appropriate α,β -unsaturated ketones with phenylhydrazine and subsequent oxidation of the resultant pyrazolines¹. This method often finds its application in the synthesis of steroidal pyrazoles² which have been synthesized by other methods also^{3,4} and screened for their biological activity^{5,6}. This paper describes our attempt to obtain some of the steroidal pyrazoles from the corresponding α,β -unsaturated ketones and phenylhydrazine. The α,β -unsaturated steroidal ketones used for the present study are 4-cholesten-6-one (I), 6-oxo-4-cholesten-3 β -yl acetate (II), 4-cholestene-3,6-dione (III) and 6 β -bromo-4-cholesten-3-one (IV).

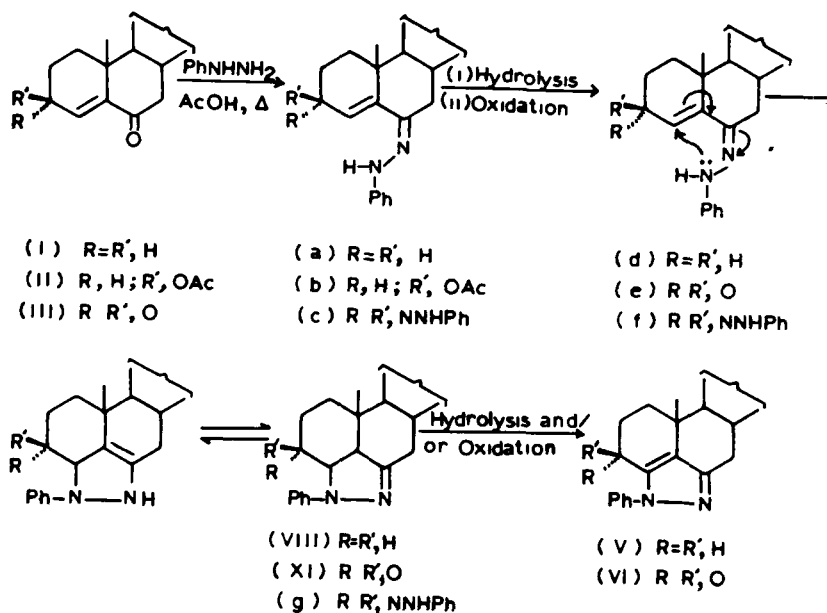
Reaction of I with phenylhydrazine in the presence of acetic acid led to the formation of 2-phenyl-4-cholesten-3-one (V). Formulation of V ($C_{33}H_{48}N_2$) was based on elemental analysis and spectral data. This composition was further supported by its mass spectrum which gave the molecular ion peak at m/z 472 ($C_{33}H_{48}N_2$). Its IR spectrum showed bands at 3050 w (aromatic C-H), 1500 s (C=N), 1600 m, 750 and 690 cm^{-1} (mono-substituted benzene)^{3,7}. Its UV spectrum exhibited an absorption band at 268 nm due to pyrazole moiety^{3,8}. The PMR signals were observed at δ 7.48 (br m, 5H, C_6H_5), 2.8 (br m, 2H, C_7-H_2), 1.9 (br m, 2H, C_3-H_2), 1.1 ($C_{10}-Me$), 0.73 ($C_{13}-Me$), 0.93 and 0.83 (other methyls). A probable mode of formation of V from I has been suggested in Scheme 1.

In order to substantiate[†] the intermediacy of the pyrazoline (VIII), the reaction of I was carried out under nitrogen atmosphere. The hydrolytic work-up of the reaction mixture gave no indication for the

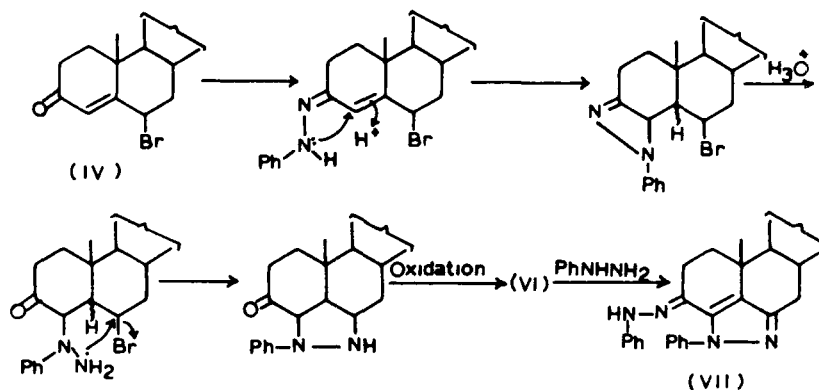


presence of V (by TLC). The crude material on rapid column chromatography gave a fraction (light petroleum-ether, 70:1) as an oil for which IR and PMR spectra were obtained hurriedly since this material showed signs of rapid deterioration. The oily compound gave IR bands at 3030 w, 1600 s, 1500 740 s and 690 cm^{-1} and the PMR spectrum displayed

[†]As suggested by the learned referee



Scheme 2



Scheme 1

signals at δ 6.9 (br *m*, C_6-H_5), 4.2 (br *m*, C_4-H), 2.7 (*d*, $J=12$ Hz, C_7-H_2), 1.1, 0.9, 0.8 and 0.63. An unresolved doublet but not accounting for one full proton was observed at δ 3.3 which could be assigned to $C_5-\alpha H$. These spectral data supported the structure VIII. Pyrazoline VIII when left at room temperature started changing into V within a couple of hours and autooxidized completely within 24 hr. The lead tetraacetate oxidation of VIII into V was found to be complete within 20 min⁹.

Interestingly, the reaction of phenylhydrazine with ketones (II-IV) gave 3-oxo-2'-phenyl-4-cholesteno[4,6-*cd*]pyrazole (VI) as one of the products in each case. The identification of VI was made on the basis of elemental analysis and spectral data. The IR bands for VI were observed at 1680 s, 1640 w, 1600 m, 1550 w, 1495 s, 750 s and 690 m cm^{-1} and the PMR signals appeared at δ 7.5 (br *m*, 5H, C_6-H_5), 2.8

(br *m*, 2H, C_7-H_2), 2.3 (*m*, 2H, C_2-H_2), 1.2, 1.1, 0.8, 0.72 and 0.66 (methyls). Its UV spectrum showed absorption maxima at 310, 258 and 226 nm. Its mass spectrum gave the molecular ion peak at m/z 486 ($C_{33}H_{46}N_2O$). These spectral data fairly supported the structure VI. The formation of the pyrazole VI from different starting materials must have occurred through different pathways (Schemes 1 and 2).

In order to obtain the precursor of VI from the three sources, the ketones II, III and IV were treated with phenylhydrazine under nitrogen atmosphere. The ketone II gave, after usual work-up and column chromatography, a fraction (petroleum-ether only) as an oil for which IR bands were obtained at 3040 w, 1620 s, 1590 m, 1480 m, 1420 m, 765 s and 690 s cm^{-1} . The PMR spectrum displayed signals at δ 7.5 (br *m*, 5H, C_6-H_5), 5.8 (br *m*, 1H, C_3-H), 2.7 (br *m*, 2H, C_7-H_2), 1.2, 1.1, 0.9, 0.8 and 0.7 (methyls). The strong

band in its IR spectrum at 1620 cm^{-1} and the PMR signal at $\delta\ 5.8$ for C_3 -vinyl proton clearly indicate a $\text{C}=\text{C}$ to be formed by the elimination of acetic acid giving rise to XII. With a view to obtaining the pyrazole V, the compound XII was treated with sodium methoxide which resulted in its $\text{C}-\text{C}$ double bond isomerization to give V. However, with *p*-toluenesulphonic acid we failed to convert XII into V.

Further elution with light petroleum-ether (55:1) afforded an unstable oily material for which only IR spectrum could be obtained as it was changing to VI as revealed by TLC. The IR bands were observed at 3060 w , 1705 m , 1600 s , 1500 s , 750 m and 690 cm^{-1} . These data are compatible with the pyrazoline structure XI. The LTA oxidation of XI converted it into VI. It is to be noted that neither the acetoxy-(IX) nor hydroxypyrazoline (X) could be isolated. However, we isolated only XI as the precursor of VI which indicated that apparently hydrolysis of the acetate function followed by oxidation of the allylic alcohol intermediate had taken place concurrently in the reaction of II.

The compound VII obtained from the reaction of IV analysed for $\text{C}_{39}\text{H}_{52}\text{N}_4$. Its mass spectrum gave the molecular ion peak at $m/z\ 576$ ($\text{C}_{39}\text{H}_{52}\text{N}_4$). Its UV spectrum showed two absorption maxima at 365 and 274 nm. The IR bands were found at 3240 w , 1590 m , 1505 m , 1605 s , 750 s and 690 s cm^{-1} . The PMR spectrum displayed signals at $\delta\ 12.7$ (s, 1H, N-H), 7.5 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 2.9 (m, 2H, C_2-H_2), 2.25 (m, 2H, C_7-H_2), 1.2, 0.9, 0.8 and 0.75 (methyls). The downfield chemical shift ($\delta\ 12.7$) for N-H is attributed to the fact that there is no vicinal coupling of N-H proton which receives further support from earlier observations^{8,10-12}. The pyrazole VII was also obtained by treating VI with phenylhydrazine.

Experimental Procedure

All melting points are uncorrected. IR spectra were determined in KBr on a Perkin-Elmer 237 spectrophotometer (ν_{max} in cm^{-1}), UV spectra in 95% EtOH on a Beckman DK-2 spectrophotometer, PMR spectra in CDCl_3 on a Varian A60 instrument with TMS as internal standard (chemical shifts in δ -scale), and mass spectra on a JMS D-300 mass spectrometer at 70 eV using the direct insertion technique at a source temperature of 250° . TLC plates were coated with silica gel and sprayed with 20% perchloric acid solution for visualisation. Light petroleum refers to fraction, b.p. $60-80^\circ$.

Reaction of I-IV with phenylhydrazine under nitrogen atmosphere: General procedure

The ketone I^{13} (1.0 g) was dissolved in dry benzene (30 ml) and to this solution were added phenyl-

hydrazine (2 ml) and gl. acetic acid (2 ml). After bubbling nitrogen gas into the reaction flask for 3-5 min, the contents were allowed to reflux under the same conditions for 3 hr. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, aq. sodium bicarbonate solution (5%) and again with water, dried (Na_2SO_4) and solvent removed. Column chromatography of the residue afforded an oily compound (VIII, 800 mg) which was oxidized to V with lead tetraacetate (*vide infra*).

Reaction of I with phenylhydrazine in air

To a solution of I (1.0 g) in benzene (30 ml) were added phenylhydrazine (2 ml) and acetic acid (2 ml). The reaction mixture was refluxed for 3 hr. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, aq. sodium bicarbonate solution (5%) and again with water, dried (Na_2SO_4) and solvent removed to give a semi-solid material which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (35:1) gave 2'-phenyl-4-cholestenol[4,6-*cd*]pyrazole (V) which crystallized from methanol, yield 400 mg, m.p. 152° (Found: C, 83.6; H, 9.9; N, 5.2. $\text{C}_{33}\text{H}_{48}\text{N}_2$ requires C, 83.9; H, 10.2; N, 5.9%).

Oxidation of VIII with lead tetraacetate

The oily material (VIII; 800 mg) was dissolved in 25 ml benzene and a few crystals of freshly prepared lead tetraacetate were added to it. The reaction mixture was heated on a water-bath for 20 min and benzene removed under reduced pressure. Usual work-up and removal of the solvent gave a semi-solid which after crystallization from methanol afforded the pyrazole V (250 mg), m.p. and m.m.p. 152° .

3-Oxo-2'-phenyl-4-cholestenol[4,6-*cd*]pyrazole (VI)

The ketone II^{14} (1.0 g) in benzene (25 ml) was treated with phenylhydrazine (2 ml) and acetic acid (2 ml) and the mixture refluxed for 4 hr. Usual work-up and removal of solvent gave a semi-solid which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (40:1) yielded VI which crystallized from methanol, yield 380 mg, m.p. 226° (Found: C, 81.1; H, 9.2; N, 2.9. $\text{C}_{33}\text{H}_{46}\text{N}_2\text{O}$ requires C, 81.5; H, 9.5; N, 2.9%).

Reaction of III with phenylhydrazine

The ketone III^{15} (1.0 g) was subjected to a similar reaction with phenylhydrazine as described for I and II. After usual work-up and column chromatography gave VI as the sole product which crystallized from methanol, yield 320 mg, m.p. and m.m.p. 226° .

Reaction of IV

The bromoketone IV¹⁶ (2.0 g) was dissolved in benzene (30 ml) and to this solution were added phenylhydrazine (2.5 ml) and acetic acid (2 ml). The mixture was refluxed for 4-6 hr. The solvent was removed under reduced pressure and the residue extracted with ether and worked-up in the usual manner. Removal of the solvent provided an oily material which was chromatographed over silica gel (60 g). Elution with light petroleum-ether (50:1) gave VII which crystallized from methanol, yield 400 mg, m.p. 195° (Found: C, 81.2; H, 9.2; N, 9.4. C₃₉H₅₂N₄ requires C, 81.3; H, 9.0; N, 9.7%).

Further elution with the same solvent system (40:1) afforded the pyrazole VI which recrystallized from methanol, yield 300 mg, m.p. 226°.

Isomerization of XII to V

The oily compound XII (100 mg), obtained from the reaction of II under nitrogen, was dissolved in benzene (15 ml) and to this solution was added sodium methoxide solution (20 ml). The reaction mixture was heated under reflux for 1 hr. Removal of the solvent and usual work-up gave the pyrazole V which crystallized from methanol, yield 65 mg, m.p. and m.m.p. 152°.

Acknowledgement

Financial assistance to S A A and S M A from the CSIR, New Delhi is gratefully acknowledged.

References

- 1 Latif N, Mishriky N & Girgis N S, *Chem Ind*, **3** (1976) 28
- 2 Bladon P, Rae D R & Tait A D, *J chem Soc Perkin-I*, (1974) 1468.
- 3 Green B, Jensen B L & Lalan P L, *Tetrahedron*, **34** (1978) 1633
- 4 Kamernitskii A V, Pavlova-Grishina N S & Shorova A V, *Izv Akad Nauk SSSR, Ser Khim*, **5** (1980) 1136, *Chem Abstr*, **93** (1980) 168477e.
- 5 Clinton R O, Manson A J, Stonner F W, Neumann H C, Christiansen R G, Clerke R L, Ackerman J H, Page D F, Dean J W, Dickinsen W B & Carabateas C, *J Am chem Soc*, **83** (1961) 1478
- 6 Hirschmann R, Buchschacher P, Steinberg N G, Fried J H, Ellis R, Kent G J & Tishler M, *J Am chem Soc*, **86** (1964) 1520
- 7 Bellamy L J, *The infrared spectra of complex molecules*, (Methuen London) 1958.
- 8 Milligan T W & Minor B C, *J org Chem*, **27** (1962) 4663
- 9 Gladstone W A F & Norman R O C, *J chem Soc(C)*, (1966) 1536
- 10 Schantl J G, Carpellus P & Pream M, *Tetrahedron*, **38** (1982) 2643
- 11 O'Connor R, *J org Chem*, **26** (1961) 4375
- 12 Zvilichovsky G & David M, *J chem Soc Perkin-I*, (1983) 11.
- 13 Heilbron I M, Jones E R H & Spring F S, *J chem Soc*, (1937) 801
- 14 Fieser L F, *J Am chem Soc*, **75** (1953) 4386
- 15 Fieser L F, *J Am chem Soc*, **75** (1953) 5421.
- 16 Ruzicka L, Bosshard W, Fischer W H & Wirz H, *Helv chim Acta*, **19** (1936) 1147.